S. HRG. 112–885

PRESCRIPTION DRUG SHORTAGES: EXAMINING A PUBLIC HEALTH CONCERN AND POTENTIAL SOLUTIONS

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TWELFTH CONGRESS

FIRST SESSION

ON

EXAMINING THE PRESCRIPTION DRUG SHORTAGES, FOCUSING ON EXAMINING A PUBLIC HEALTH CONCERN AND POTENTIAL SOLUTIONS, AND IF THE FOOD AND DRUG ADMINISTRATION'S ABILITY TO RESPOND SHOULD BE STRENGTHENED

DECEMBER 15, 2011

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C O N T E N T S

STATEMENTS

THURSDAY, DECEMBER 15, 2011

ADDITIONAL MATERIAL

PRESCRIPTION DRUG SHORTAGES: EXAMINING A PUBLIC HEALTH CONCERN AND POTENTIAL SOLUTIONS

THURSDAY, DECEMBER 15, 2011

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:05 a.m. in Room 106, Dirksen Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Mikulski, Bingaman, Casey, Hagan, Merkley, Franken, Bennet, Whitehouse, Blumenthal, Enzi, Isakson, Hatch, and Kirk.

Also Present: Senator Klobuchar.

OPENING STATEMENT OF SENATOR HARKIN

The CHAIRMAN. Good morning. The Senate Committee on Health, Education, Labor, and Pensions will come to order.

Today's hearing focuses on a serious public health issue in the United States. That's the growing problem of prescription drug shortages. For the past several years, hospitals across the country have experienced an increasing number of shortages of life-sustaining prescription drugs. Today we're going to examine the cause of the shortages and explore potential solutions.

The harsh reality is, the problem is getting dramatically worse. The number of prescription drug shortages in the United States has tripled over the past 5 years. Over 80 percent of these shortages involve generic sterile injectables, including critical products used for chemotherapy, emergency medicine, anesthesia, and intravenous feeds. Many of these products are absolutely essential for the treatment of serious diseases, and shortages in anesthetic products are adversely affecting even the most routine surgeries.

As hospitals encounter difficulties in securing an adequate supply of critical drugs, it forces doctors to ration their supply of medication, delay medical procedures, and use alternative products that may have unwanted side effects. In some instances, drug shortages also compel medical practitioners to rely on foreign versions of drugs that have not been reviewed by the FDA and not approved for use in the United States.

For patients, drug shortages can literally be a matter of life or death. To cite one example, Al Wegner of Ionia, IA wrote to inform me that a drug he received to treat his colon and prostate cancer is now in shortage and will run out by the end of the year.

In May, Senator Enzi and I convened a bipartisan working group to evaluate the issue of shortages and identify potential legislative solutions. Between the work of that group and our discussions today, I'm hopeful that we can agree on meaningful bipartisan solutions to address this complex problem.

In May, along with Senators Casey and Blumenthal, I wrote to the Government Accountability Office to request a report on the drug shortage problem and potential solutions. GAO issued its report this morning. Marcia Crosse, Director of GAO's health care team, is here to discuss that, including its recommendations.

I also look forward to hearing from our other witnesses who bring to this discussion a wide range of experiences and perspectives, and I thank you all for being here.

I also want to acknowledge and thank our distinguished Ranking Member, who has been a key leader here in the Senate in addressing this issue.

I will yield to Senator Enzi for an opening statement.

OPENING STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman. Thanks for having this hearing.

As a result of recent drug shortages, patients all over the United States are forced to delay their treatment or use second-best alternatives. Clinical trials that use these drugs are being stalled, preventing possible new treatments from coming to market. The pharmaceuticals in shortage are complex to manufacture and treat a variety of conditions in different settings. They have always been vulnerable to shortage. However, these shortages are now more widespread.

Currently, FDA lists over 200 products in short supply. These shortages result in increased costs for patients, the Government providers, researchers, and worse outcomes for patients. Generic drugs make up the majority of drugs in shortage, and many are inexpensive. While we must move as quickly as possible to get these life-saving drugs to the patients that need them, it's important that we understand the causes that lead to this tragic problem.

There are conflicting opinions on how economics, regulation, and supply-chain management contribute to the shortages we see today. I understand this is a complex, multifaceted issue, and I look forward to hearing from all our witnesses today to help clarify the root causes and describe possible next steps.

Only once we understand the causes should we craft a solution. There are many alternative policy options being discussed. My colleague, Senator Klobuchar, and Senator Hatch have been leaders in this area, but their proposals address very different problems. We must keep in mind possible unintended consequences as we move forward.

My staff has been participating on a bipartisan working group for months, meeting with the stakeholders, investigating the causes, and developing solutions. I look forward to seeing the group's proposal in the next few months. I understand that the generic pharmaceutical industry is also working to come up with a solution to address supply interruptions as well, and I look forward to hearing more about that today.

There is bipartisan desire to implement a solution that will not only mitigate shortages in the short-term but address underlying causes so we don't find ourselves in this tragic situation again. I look forward to working with my colleagues on and off the committee to do this as quickly as possible without compromising the quality of the policy.

I'm concerned, however, that the FDA could be doing more to address these shortages now. The Government Accountability Organization says their management remains a barrier, and new record-keeping methods would not improve communication within the agency. Further, GAO says there has not been a systematic review of all applications currently waiting for approval to see if they are relevant to the shortages.

As a first step, FDA should expedite the review of any application for drugs in shortage. I find it troubling that we do not know how many applications relevant to shortages are waiting for FDA review and look forward to exploring any barriers that are currently preventing the agency from identifying and expediting these applications.

That being said, I want to commend the work of the Drug Shortages Office of the Food and Drug Administration. Until recently, this office only had four members. Yet, when provided information about shortages, they have been able to assist in communication and finding solutions with the manufacturers in some cases. I only hope that this sort of collaboration among offices in FDA and industry will continue after the public health emergency is resolved.

Looking back a few years, multiple companies shut down capacity at the same time. Increased coordination may have helped to prevent some of the situations we find ourselves in today.

Thank you for convening this important hearing, and I look forward to discussing what steps we can take to solve this tragic problem.

The CHAIRMAN. Thank you very much, Senator Enzi.

We'd like to start off by welcoming our esteemed colleague, Senator Klobuchar from Minnesota. She's been a leader in this effort and has introduced an important bill on this issue with Senator Casey. It's called the Preserving Access to Life-Saving Medications Act.

Senator Klobuchar, we're pleased to have you here this morning. Your statement, of course, will be made a part of the record in its entirety, and please proceed as you so desire.

STATEMENT OF SENATOR KLOBUCHAR

Senator KLOBUCHAR. Thank you very much, Chairman Harkin, Ranking Member Enzi, Senator Kirk. Thank you very much for starting the working group and being devoted to doing something about this issue. It's something that experts are seeing as an unprecedented shortage in drugs, forcing some patients to delay their treatments, using unproven alternatives or, sadly in some cases, drug shortages have even resulted in patient deaths.

Over a year ago I heard about this first. I think Senator Harkin, from the Midwest, understands our people are loud and call their officials when things go wrong, and I couldn't believe the number of pharmacists, and also doctors and patient groups, that came to

our office seeking help. And as the year went on, I think more and more of my colleagues heard about this from people in their own States.

Just a few months ago I met a young boy named Axel Zirbes. Alex Zirbes is a little 4-year-old boy with bright eyes and a big smile. He also happens to have no hair on his head, and that's because he's being treated for leukemia. When he was scheduled to start chemotherapy earlier this year, Axel's parents learned that an essential drug, cytarabine, was in short supply and might not be available for their son. Obviously, this threw them into a panic. They started calling themselves all over the country. The pharmacists were trying, the doctors were trying, and they actually made plans to go to Canada so he could get his chemotherapy treatment.

Well, at the last minute, the hospital was able to secure the medication from a pharmacy that still had a supply. But I think you all know, Axel and his parents are not alone, and not every story has turned out as good as that one.

As you know, there were 178 drug shortages reported in 2010 and already 231 reported as of this November. Look at that dramatic increase. When you go back 5 years, there were only 55 drug shortages. So the facts speak for themselves.

For some of these drugs, no substitutes are available. Or, if they are, they're less effective. A survey conducted by the American Hospital Association showed that nearly 100 percent of their hospitals experienced a shortage.

It is clear that there are a large number of overlapping factors, as Senator Enzi discussed, that are resulting in unprecedented shortages. Experts cite a number of factors. Market consolidation and poor business incentives, manufacturing problems and production delays, unexpected increases in demand for a drug, inability to procure raw materials, and even the influence, the very unfortunate influence as of late, of a "gray market."

However, when drugs are made by only a few companies, a decision by one drug maker can have a large impact.

Therefore, to help correct a poor market environment or to prevent "gray market" drugs from contaminating our medication supply chain, we must address the drug shortage problem at its root.

As was mentioned, I introduced the Preserving Access to Life-Saving Medications Act with Senator Casey of Pennsylvania. Susan Collins joined us, and many others, and so the bill now has bipartisan support. The bill would require drug manufacturers to provide early notification to the FDA whenever there is a factor that may lead to a shortage.

And I would agree with Senator Enzi that it's very complicated to look at what these causes are and to figure out the long-term solutions. But I believe that the short-term solution has already been proven to work. When you look at the numbers with the FDA, in the last 2 years the FDA, with early notification and more information, has successfully prevented 137 drug shortages.

So when we went to them to try to figure out what we can do to at least address this immediate problem, they said, "Look, what we're doing works, but we don't really necessarily have the tools and the authority to be able to do this across the board," and that's

why we came up with the idea of doing it beyond orphan drugs to doing it sooner so that they get the information sooner, because the sooner they get the information, the more they're going to be able to respond and get something done.

In addition to adding more sponsors and the good working group that you've set up since the time that we introduced this bill, two major things have happened. The administration, the President has endorsed this bill. The House has taken on a very similar bill, led by Representative DeGette. The President's Executive order, I should note, took steps toward advancing the goals. But he made clear at the same time that Congress must still act in order to protect patients and ensure consumers have access to these life-saving medications.

The second major change is that today the FDA is announcing a rule that would expand shortage notification for sole-source manufacturers. This is clearly a step in the right direction, but I would argue we still need to get this legislation done because we have the issue that we have manufacturers that are not sole-source that have also been involved in drug shortage situations. So there is good reason to continue to work to pass this legislation.

And then it also has been noted by both the Chairman and the Ranking Member that we need to continue the work of the working group to look at the long-term solutions to this problem.

I would just add when you look at the eyes of that little 4-year-old balding boy and you realize that his whole family was put in a panic, or you meet some of the patients that I've met, or the pharmacists who are already under-staffed and are dealing with very difficult times in health care, the last thing we want to do is to have hospitals, doctors, or pharmacists running around literally spending half a day trying to find one dose of a medication. This is no way to run a railroad.

I really appreciate the committee's willingness to look at this issue. I would urge you to move our legislation as soon as possible as a short-term solution, and then continue the long-term work that needs to be done to get at the underlying root causes of this problem.

Thank you very much, Mr. Chairman, for allowing me to speak today. Thank you for all the Senators that have come today. We now have six of you here, so I know we can solve this problem, and I look forward to working with all of you. Thank you very much.

[The prepared statement of Senator Klobuchar follows:]

PREPARED STATEMENT OF SENATOR KLOBUCHAR

Chairman Harkin, Ranking Member Enzi, and my fellow colleagues on the HELP Committee—I am glad that this hearing is being held today to discuss causes and solutions to the drug shortage crisis. I appreciate the opportunity to join you all and briefly share my thoughts and experiences after having worked on this issue for the past year.

The country is facing what experts are calling a "crisis" with "unprecedented" shortages for a record number of essential drugs. Drug shortages have impacted individuals all across the country—forcing some patients to delay their life-saving treatments or use

unproven, less-effective alternatives. In some cases, drug shortages have even resulted in patient deaths.

Because of the urgency of this issue, this morning the FDA announced an Interim Final Rule that will require manufacturers to provide early notification to the FDA so the agency can work with manufacturers, hospitals, pharmacists, and patients to find ways to prevent drug shortages.

Having this information will help FDA take steps necessary to find appropriate alternatives, aid manufacturers in correcting manufacturing problems, and help providers and patients maintain the care they need and deserve.

The legislation that I introduced with Senator Casey, *The Preserving Access to Life-Saving Medications Act*, would require drug manufacturers to provide early notification to the FDA whenever there is a factor that may lead to a shortage. And it is helpful that the FDA followed our leadership and took the steps they did today to speed this process along.

This is something I have been working on for over a year when I first heard from hospitals, pharmacists, and patients from Minnesota that they were facing shortages in essential medications—specifically to chemotherapy drugs. Their urgency caused me to send a letter to FDA Commissioner Hamburg urging the FDA to take actions to address this public health crisis.

Over the next few months, I continued to receive calls from constituents asking for help in finding medications in short supply. I worked with manufacturers, stakeholders, and the FDA to try to find an appropriate solution to ensure that patients continued to receive the care they needed and deserved.

Just a few months ago, I met a young boy named Axel Zirbes. Axel Zirbes is a cute 4-year-old boy from the Twin Cities with bright eyes and a big smile. He also happens to have no hair on his head. That's because Axel is being treated for leukemia.

When he was scheduled to start chemotherapy earlier this year, Axel's parents learned that an essential drug, cytarabine (sye-TARE-a-been), was in short supply and might not be available for their son. Understandably, they were thrown into a panic and desperately looked for any available alternatives. They even prepared to take Axel to Canada, where cytarabine (sye-TARE-a-been) was still readily available.

Fortunately, it didn't come to that. At the last minute, the hospital was able to secure the medication from a pharmacy that still had a supply.

But Axel and his parents are not alone.

As you know, there were 178 drug shortages reported in 2010 and already 231 reported as of this November—a dramatic increase from 55 just 5 years ago.

For some of these drugs, no substitutes are available. Or, if they are, they're less effective and may involve greater risks of adverse side effects. The chance of medical errors also rises as providers are forced to use second- or third-tier drugs that they're less familiar with.

A survey conducted by the American Hospital Association showed that nearly 100 percent of their hospitals experienced a shortage. Another survey, conducted by Premier Health System,

showed that 89 percent of its hospitals and pharmacists experienced shortages that may have caused a medication safety issue or error in patient care.

It is clear that there are a large number of overlapping factors that are resulting in unprecedented shortages. Experts cite a number of factors that are responsible for the shortages. These include market consolidation and poor business incentives, manufacturing problems and production delays, unexpected increases in demand for a drug, inability to procure raw materials, and even the influence of the "gray market".

However, when drugs are made by only a few companies, a decision by any one drugmaker can have a large impact.

Therefore, to help correct a poor market environment or to prevent "gray market" drugs from contaminating our medication supply chain, we must address the drug shortage problem at its root.

As I mentioned, the bill I introduced with Senator Casey will require manufacturers to provide early notification to FDA. But it will also direct the FDA to provide up-to-date public notification of any actual shortage situation and the actions the agency would take to address them.

Additionally, the bill requires the FDA to develop an evidence-based list of drugs vulnerable to shortages and to work with the manufacturers to come up with a continuity of operations plan to address potential problems and add redundancies to protect against potential shortages.

The bill would also direct the FDA to establish an expedited reinspection process for manufacturers of a product in shortage.

With manufacturers providing early notification, the FDA's Drug Shortage Team can then appropriately use their tools to prevent shortages from happening. In the last 2 years, the FDA, with early notification and more information, has successfully prevented 137 drug shortages.

And while the Executive order the President issued in October took steps toward advancing these goals, he has made clear that Congress must act in order to protect patients and ensure consumers have access to the life-saving medications that they need and deserve.

I understand that this may be a short-term solution to a long-term problem. That's why I have been working with several of my colleagues on this committee to come up with a broad, permanent solution—one that includes methods to address the root causes of drug shortages.

At the urging of this bipartisan working group, the FDA held a public workshop in September that brought together patient advocates, industry, consumer groups, health care professionals, and researchers to discuss the causes and impact of drug shortages and possible strategies for preventing or mitigating future shortages.

In addition to the workshop, I have been speaking with a broad range of stakeholders to try to discover why we have seen such a large number of shortages over the past few years.

I have also urged FDA to improve their communication with patients and providers. This will ensure that patients and doctors are not the last to know when there is a shortage.

This current explosion of shortages appears to be a consequence of a lack of supply of certain products to keep up with a substantial expansion in the scope and demand for those products.

Due to the complex nature of these drug shortages, there is no single or simple solution that will solve all problems. A solution will require all stakeholders to play a role in mitigating future drug shortages.

That includes increased and transparent coordination between the offices in the FDA responsible for drug shortages, compliance, and new drug applications.

That includes better recordkeeping and communication between the drug manufacturers and the FDA.

And it must include methods to ensure that we have the manufacturing capabilities to keep up with demand. One solution may be to provide tax credits to incentivize manufacturers to upgrade their production capabilities or to remain in or join the market.

But one thing is clear: This is a national public health crisis that must be addressed. I will continue to work with my colleagues in the committee and in the Senate to try to develop a broad and permanent solution and urge my colleagues to support this legislation that will help ensure access of needed medications for our Nation's patients.

Thank you.

The CHAIRMAN. Senator Klobuchar, thank you very much for your statement and your leadership on this issue.

I know you have other committee business that you have to attend to, so thank you very much for being here, and we look forward to working with you as we try to resolve this issue.

Senator KLOBUCHAR. Thank you.

The CHAIRMAN. Thanks, Senator Klobuchar.

I thought I would call the first panel up, and that would be Dr. Sherry Glied, Dr. Sandra Kweder, and that's it, those two up for our first panel.

Before I do that, we have usually a rule in this committee that we don't have opening statements and stuff, but I know this is an issue that a lot of people have weighed in on and have great concerns about, and I thought I would allow Senators, if they would like, to make short comments on this before we turn to our panel.

[Pause.]

So, I would yield. The order of appearance is Senator Kirk, Senator Franken, Senator Merkley, Senator Isakson, and Senator Bennet.

If you had a short comment, I'd be more than willing to entertain comments, Senator Kirk.

STATEMENT OF SENATOR KIRK

Senator KIRK. Thank you. I very much appreciate this hearing. An ex-staffer of mine was just diagnosed with lymphoma type B. As everyone knows who fights that, you take a four-drug regimen called R-CHOP, and that includes doxorubicin, which is generic, only three suppliers, and in short supply. And so I'm very much looking forward to this hearing. I applaud Senator Klobuchar's legislation.

We want to make sure that the very large FDA bureaucracy does not generate a decision, because of manufacturing regulations or others, that issues a completely unbalanced decision to shut down supply, so that the patient that I know so well does not have doxorubicin to fight lymphoma.

And so I applaud you, and I think this is a very important hearing and hope to back legislation on this. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Kirk. Thanks for your leadership on this.

Senator Franken, I want to thank you also for your leadership on this issue. You've been heavily involved in this, and I appreciate it. Any comments?

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman. I'm glad to have the opportunity to discuss this critical problem, and I want to thank my senior Senator, Senator Klobuchar, for her leadership on this.

As you know, prescription drug shortages are affecting the care that patients in Minnesota and across the Nation receive, and in some cases it is truly a matter of life and death, as Senator Kirk so personally discussed.

I recently talked to a doctor from Minnesota who told me that a chemotherapy that she uses with her patients is currently in shortage. For new patients, she's going to have to recommend a treatment that may not be as effective, and for patients currently on the chemo, she's going to have to switch them to a different treatment. She told me that when she has to change a patient from a chemo that is working to a new treatment, the new chemo has only a 1 in 3 chance of working the first time, 1 in 3. Imagine telling that to your patient. Imagine being the patient.

As I'm sure we'll hear from the expert witnesses, this issue is not simple. There is no one cause or one solution. I am proud to participate in a bipartisan working group of members of this committee that is looking at legislative proposals to address these critical shortages, and I am a co-sponsor of the legislation introduced by Senators Klobuchar and Casey that will require drug manufacturers to let the FDA know when they may discontinue a drug. This legislation is an important first step while we work toward ways to address this issue on a larger scale.

Mr. Chairman, thank you again for holding this important hearing. I look forward to hearing the expert testimony today and to continue to work with you to preserve access to life-saving drugs in Minnesota and across our Nation. Thank you.

The CHAIRMAN. Thank you, Senator Franken.

Senator Merkley.

STATEMENT OF SENATOR MERKLEY

Senator MERKLEY. Thank you, Mr. Chairman. Thank you for sponsoring this hearing. I applaud Senator Klobuchar and Senator Casey for helping highlight this issue, put a spotlight on it. It's certainly of extreme concern in the health care system throughout the country.

In November I held a roundtable discussion at the Oregon Health and Sciences University to hear from Oregonians who have been directly impacted. I heard from a patient who was 6 months into his treatment for multiple myeloma when he was suddenly told that the drugs were no longer available. And at first it was you can't come in this day of the week, come in 2 days later; and then it was they're not available at all. And this is happening thousands of times a week across this Nation.

Suddenly you have a patient in the middle of a drug regimen. The spouse is wondering what can I do to help acquire these medicines. Do I get on the Internet? Do I call hospitals throughout this country? The patient, who should be focusing all of their mental energy on healing, is suddenly extraordinarily stressed, the worst possible situation for actually healing and taking advantage of the regimen.

It isn't just that it's stressful. It's that it possibly destroys the effectiveness of the treatment regimen both because of the unavailability and because of the stress.

And certainly doctors and pharmacists express that getting access to drugs that are in shortage takes up an extraordinary amount of their time and energy, which is hugely inefficient for the system. They also talked about how, over the last couple of years, the situation has gotten so much worse that there have been changes, and that's what this hearing is about, understanding it better, because it's absolutely counter-productive and unacceptable.

I look forward to hearing from the experts and working with my colleagues on both sides of the aisle who expressed a lot of concern about this. Thank you.

The CHAIRMAN. Thank you, Senator.

Senator Isakson.

STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. I commend you on calling the hearing. This is a preeminent issue in my State of Georgia.

The CHAIRMAN. Thank you, Senator Isakson.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman and the Ranking Member. Thanks for holding this hearing. It's actually been great to hear the comments from my colleagues up here because we are seeing exactly the same thing in Colorado. You know, the FDA has been notified about 220 drug shortages this year, and we know that the number of patients this affects is monumental. For cancer alone, over 550,000 patients are currently affected by our national drug shortage crisis.

In Colorado, I can tell you that our patients and providers are extremely frustrated. A pharmacist at St. Mary's Hospital in Grand Junction told us that he keeps a 2-page list of 50 drugs that he can't get or barely can get hold of, including 12 chemotherapy drugs. Our own Colorado Cancer Research Program has held public forums in places like Denver and Colorado Springs with hundreds

in attendance, trying to mobilize advocates and find consensus around solutions.

Like everyone else on this panel, I have gotten letters and calls from people suffering from cancer in my State saying what are you doing about these drug shortages? The last thing that people who are suffering from cancer should be doing is spending time having to call their Senators to say how do I get my drugs.

Mr. Chairman, this is a vital issue, a critical problem in all of our States, and I think we need to come together in the HELP Committee in a bipartisan way and make sure we're addressing it. We will continue to provide you and the Ranking Member with the work that's being done in Colorado in the Drug Shortage Working Group with additional ideas for consideration. I look forward to the testimony today.

Thank you, Mr. Chairman, for holding what I consider one of the most important hearings we've had since I've been here.

The CHAIRMAN. Thank you, Senator Bennet.

Senator Bingaman, any statements or any comments?

STATEMENT OF SENATOR BINGAMAN

Senator BINGAMAN. Mr. Chairman, I will not have comments. I look forward to the hearing and congratulate you for calling the hearing.

The CHAIRMAN. Thank you very much.

Senator Blumenthal.

STATEMENT OF SENATOR BLUMENTHAL

Senator BLUMENTHAL. I also look forward to the hearing and want to thank the Chairman for having it. It is a subject that certainly impacts Connecticut, where the workhorse medicines—and that is a term that the docs have used in describing them to me—are chronically in short supply. Our hospitals are scrambling to meet the needs of patients.

I have read the testimony that we are going to be presented today, and I have to say right at the outset that I think that much more drastic and far-reaching and aggressive measures are necessary than have been proposed in any of the testimony, any of the GAO report that has been submitted so far.

We have a working group here that has been laboring on this issue, but I am determined that at least I will be proposing more aggressive measures that are necessary to crack down on what appear to be anti-consumer practices.

This market is simply not working. It cannot be allowed to continue in the dysfunctional fashion that it is right now. It is in many respects similar to the kind of monopolistic or oligarchic markets that we've seen in other areas where essential products are, in effect, manipulated according to price and supply, and these are essential products.

The shortages are creating a public health menace, and the anti-consumer practices clearly promote a gray market, so-called gray market that drastically inflates prices and contributes to the shortages. We ought to have zero tolerance for this kind of profiteering and price gouging, and we ought to do whatever is necessary to as-

sure supplies, adequate supplies of these drugs. Whether it's oncology or anesthesiology, these drugs are needed and they should be provided, and stronger governmental action seems to be absolutely necessary.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Blumenthal.

Senator Whitehouse.

STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Mr. Chairman, thank you. I just wanted to add to the record of these proceedings that in Rhode Island, we're getting reports that it tends to be vulnerable populations that are going without or facing the risk of not having the prescription drugs that they need.

We've heard from the medical society that pediatricians are feeling a particular pinch, and one particular Rhode Island institution that we are very proud of is Women and Infants Hospital, which is really renowned throughout the region. We have people fly in from other States and countries to take advantage of the highly specialized care available there. It is a world-class facility, and they are facing drug shortages in chemotherapy, in anesthesia, and in things as simple as parent-child nutrition, potassium and magnesium, things like that.

There's a drug called doxil that is in such short supply that Women and Infants now has a waiting list for new cancer patients that require that drug, and to meet their existing need they've had to go into the gray market that Senator Blumenthal referred to, which is way above market price and is a market in which people believe a certain amount of hoarding and gaming for price gouging purposes is taking place.

This is hitting home in Rhode Island, and so I'm very grateful to you, Mr. Chairman, for holding this hearing. Thank you.

The CHAIRMAN. Thank you, Senator Whitehouse.

I thank all the Senators. This is such an important issue, I just thought it worthwhile for every Senator to express himself on this issue before we get to our panels, and so I appreciate that very much.

We'll call our first panel. Dr. Glied and Dr. Kweder, please come to the table. I have Dr. Glied on this side and Dr. Kweder on that side.

Our first witness is Dr. Sherry Glied, the Assistant Secretary for Planning and Evaluation with U.S. Department of Health and Human Services. Dr. Glied provides guidance and economic analysis to the Department on Health Policy. In October her office issued a report entitled Economic Analysis of the Cause of Drug Shortages.

She has previously served as a senior economist for health care policy on the President's Council of Economic Advisors under Presidents Bush and Clinton.

Dr. Glied, we thank you for being here today.

Next we have Dr. Sandra Kweder, Deputy Director of the Office of New Drugs in the Center for Drug Evaluation and Research in the Food and Drug Administration. As you can tell by her uniform, Dr. Kweder is a career public health officer who works on a daily

basis at FDA to ensure that drugs we use in this country are safe and effective for their intended uses. Her duties also include supervising FDA's Office of Drug Shortages.

We have two people who are quite knowledgeable about this issue, and we appreciate your being here.

We'll start with you, Dr. Glied.

I'll just say, both of your statements will be made a part of the record in their entirety. If you could sum up in 5, 6, 7 minutes, we'd appreciate it. Then we can get into a discussion.

Dr. Glied, please proceed.

STATEMENT OF SHERRY GLIED, Ph.D., ASSISTANT SECRETARY FOR PLANNING AND EVALUATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, WASHINGTON, DC

Ms. GLIED. Thank you, Mr. Chairman, members of the committee. I'm honored to be here today to discuss the work we've been doing at ASPE on the economics of this terrible problem of drug shortages, and I'm going to confine my remarks today to just two points.

First, why are there shortages in the market for some medically necessary drugs when shortages are not a feature of the U.S. economy in general? We don't usually see those in other markets.

Shortages of most products in most markets lead prices to rise, and those increases in price cause consumers to buy less of a product, and they lead producers to manufacture more of it. That process does not happen in these markets.

The problem is not the prices. Our analyses show that the prices of drugs in these markets do rise in response to shortages in just the same way they do in other markets. But these short-run price increases have very little impact on either the demand for these products or on their supply.

On the demand side, by definition, these drugs are medically necessary, so treatment patterns don't change very much even when prices rise, and that's what we would like to see.

On the supply side, the kinds of drugs that we now see in shortage are produced using costly, very specialized equipment. Building a new production line and increasing capacity in this market takes several years and can cost hundreds of millions of dollars. In the short run, manufacturers can and do respond to price increases by switching among the approved product within a class using the same production line or factory. So if you think about these production lines, they can produce many different drugs within a class, and the manufacturers can switch among them.

Unfortunately, switching among products often just shifts the shortage from one drug in a class to another drug in the same class.

Manufacturers can also respond to price increases by increasing the level of capacity utilization in their plants, moving from, say, two shifts a day to three. But we've learned that most manufacturers in this sector today are operating at full capacity, essentially 24/7, and operating 24/7 can limit their ability to keep their plants in good working order and may be contributing to the quality problems that we're seeing in this sector.

Now, in the longer run, manufacturers can expand capacity if they see a profitable market ahead of them. In our analyses, we found that the market for sterile injectable generic drugs, cancer drugs in particular, is robust and is growing. Over the last 5 years, the size of the overall generic sterile injectable market expanded by over 50 percent, and they anticipate to grow even further. And manufacturers are responding to this anticipated growth. Several have told us that they are investing substantially to upgrade existing facilities and to build new facilities to serve this growing market. Those facilities are not likely to be online for the next year to 3 years, however.

The second point I wanted to touch on is the source of the prices in this market. Unlike the situation with most drugs in the United States, sterile injectable drugs are not purchased directly by patients, and they are not reimbursed directly by insurance. Rather, these drugs are purchased by health care providers, by doctors and hospitals, who are paid for the delivery of the service that includes the drug, and they are sometimes also paid a separate fee to compensate for the cost of procuring the drug. They obtain the drugs, in turn, through group purchasing organizations, which negotiate prices with manufacturers on behalf of their clients.

Group purchasing organizations compete among themselves to negotiate the lowest possible price at which they can get an adequate supply of drugs from manufacturers. That single negotiated price applies to the hospital or physician's purchases of that drug regardless of the insurance held by the patient who ultimately uses the drug.

As we think about strategies to address this problem of shortages, it's important to keep in mind these two points, first, that supply across the sector does not increase in the short run in response to price increases, and that there is a very sharp disconnect between the fees paid to providers and the amount that group purchasing organizations pay to manufacturers.

In summary, our analyses suggest that the current shortages will likely be fully resolved only when new supply sources come online. In the meantime, managing shortages effectively in the short run, as the FDA's Drug Shortage Program is doing, is likely to be the best approach to addressing this serious public health problem.

Thank you. I'd be happy to take any further questions.

[The prepared statement of Ms. Glied follows:]

PREPARED STATEMENT OF SHERRY GLIED, PH.D.

INTRODUCTION

Mr. Chairman and members of the committee, I am Dr. Sherry Glied, Assistant Secretary for Planning and Evaluation at the U.S. Department of Health and Human Services. I am honored to be here today to discuss the economics of drug shortages.

For some patients, a change in treatment regimen because an important medication is not available can seriously reduce the quality of care they receive and threaten their ability to get better. We have heard the stories of a number of people who have faced this problem. Patients, like Jay Cuetara, a cancer patient from California with whom I met earlier this fall, are the ones who suffer when the center where they receive chemotherapy runs out of the drugs used to treat their cancer.

The Food and Drug Administration (FDA) has successfully prevented 233 drug shortages since the beginning of 2010 and is taking additional actions to address drug shortages in response to the President's October 31 Executive order. In the 4

weeks following the issuance of the Executive order, FDA has received 61 notifications, a sixfold increase over the average notifications per month in the previous 10 months.

Drug shortages have been increasing in frequency and severity in recent years and are adversely affecting patient care. A small number of drugs in the U.S. experience a shortage in any given year, but the number of reported prescription drug shortages in the United States has nearly tripled between 2005 and 2010, increasing from 61 to 178. In 2011, FDA has continued to see an increasing number of shortages, particularly among older sterile injectable drugs, including cancer drugs, anesthetics for surgery, drugs for emergency medicine, and electrolytes for intravenous feeding. There are many causes to this challenging problem and addressing this significant public health threat requires the urgent attention of industry, other stakeholders, and government.

BACKGROUND

Market Behavior

Firms have been increasing their levels of manufacturing capacity utilization to accommodate the increase in the volume of chemotherapy drugs administered and the expansion of products available for generic manufacturing because of patent expiration. Shortages have been concentrated in drugs where the volume of sales was declining in the years preceding the shortage, suggesting that manufacturers are diverting capacity from shrinking lines of business to growing ones. Quality problems, potentially caused by the high level of capacity utilization, have led some plants to shut down. A recent report by FDA found that quality problems at drug manufacturing facilities resulting in disruptions in supply were the leading cause of drug shortages, accounting for 43 percent of all shortages. Firms have not responded quickly to changes in demand and prices in the sterile injectable drug industry by building new plant capacity because of the high fixed costs of specialized production. Furthermore, because shortages are generally uncommon and occur in drugs for which capacity is highly specialized, and because there are few penalties for failing to supply contracted drugs, there is no financial return to manufacturers from investing in excess capacity—that is, capacity that is not used outside a supply shortage, and thus earns no revenue except during a supply shortage.

Generic drug manufacturers must make strategic decisions about how to deploy existing production capacity among products, based on their expectations about what choices their competitors will make and what demand will be. In general, manufacturers will prefer to concentrate on markets with fewer competitors, where they are likely to face less price competition. Conversely, purchasers, such as GPOs, will prefer that multiple competitors produce each product. If manufacturers misjudge their competitors' choices, there may be excess supply and depressed prices for some drugs and insufficient supply and shortages of others. In small markets, such as those for sterile injectable drugs, these decisions can lead to considerable volatility in the market.

WHY DO SHORTAGES OCCUR IN THE PRESCRIPTION DRUG MARKET?

The prescription drug and vaccine market is characterized by sporadic shortages of individual drugs and occasional periods during which many drugs in a class are in shortage. Although product shortages usually lead prices to rise, consumers to buy less, and producers to manufacture more, that process does not happen in the markets for some medically necessary drugs, especially sterile injectable drugs. By and large, neither the supply nor the demand for medically necessary drugs responds quickly when the prices of these drugs rise.

By definition, these drugs are medically necessary, so they have few substitutes and patients cannot generally shift their use over time. Unlike consumers of other goods and services, patients, hospitals, and physicians generally do not change treatment patterns when prices rise.

Suppliers are also quite insensitive to changes in price, particularly in the short-run. The kinds of medicines that are in shortage are produced using costly, specialized equipment and require complex production processes that must meet Current Good Manufacturing Practice guidelines. Manufacturers can and usually do substitute products within a class using the same production line, but in most cases, each individual drug requires regulatory approvals, including manufacturing controls, which are limited to that particular drug. It generally takes a long time—years in some cases—for the industry to increase capacity in response to an increase in prices. If the increase in prices is expected to be temporary (as would be expected in the case of a shortage due to a production line disruption), investments in in-

creased capacity are unlikely to occur. In the longer run—over a period of 2–3 years, for example—supply will be much more responsive to price.

This low level of price responsiveness on both the demand and supply sides of the market for many medically necessary products means that any changes from historical patterns in supply or demand can lead to shortages of these drugs.

THE CASE OF STERILE INJECTABLE CANCER DRUGS: SUPPLY AND DEMAND

In most cases, sterile injectable drugs are not purchased directly by patients or reimbursed directly by insurance. Rather, these drugs are purchased by health care providers (generally hospitals and physicians). Providers are paid for the delivery of the service that includes the drug. Public and private insurers also pay a separate fee to compensate for the cost of the drug. Under the Medicare program, the separate fees for sterile injectable drugs generally are paid under Part B.

Most hospitals and physicians do not purchase sterile injectable drugs directly from the manufacturer. Rather, these drugs are purchased through group purchasing organizations (GPOs), which negotiate prices with manufacturers on behalf of their clients. GPOs do not take physical possession of the drugs. Instead, a wholesaler takes possession of the drug and then sells the drugs to hospitals and physicians at the GPO negotiated price.

While GPOs negotiate the lowest prices they can with manufacturers, based on anticipated volume of sales, their clients are not compelled to purchase drugs from a contracted manufacturer, so the GPO contracts do not necessarily contain minimum quantity guarantees. GPO contracts are generally in place for years and typically include price adjustment clauses. If a GPO is offered a lower price by a competing manufacturer, the original contracted manufacturer has a right of first refusal to match the new price. GPO contracts also typically include failure-to-supply clauses. These clauses generally require the manufacturer to reimburse the GPO for the difference between the negotiated price and the purchased price when providers must buy the drug from another source. These failure-to-supply clauses, however, provide no reimbursement if there are no alternative sources for the drug, do not reimburse for resources expended looking for other sources, and are of limited duration.

Manufacture of generic sterile injectable drugs is a concentrated market with 7 manufacturers making up a large percentage of the market. Most of the production of a given drug is by three or fewer manufacturers. Analysis of a sample of 33 generic sterile injectable cancer drugs shows that for 28 of these drugs, at least 90 percent of unit sales in 2010 were made by three or fewer manufacturers.[1] These manufacturers typically each operate a small number of facilities at which injectable drugs can be produced. These facilities, in turn, each contain several manufacturing lines. A particular drug can be produced on one or more of these lines in runs that may last from hours to weeks. The same line may be used for multiple different drugs produced in separate batches; however, certain drugs (including cytotoxic drugs) may only be produced on certain types of lines and in certain types of facilities, so the extent of substitution is limited.

It is important to note that the low price responsiveness of demand for sterile injectable drugs also has implications for inventories and capacity decisions. If there is an excess supply of a particular drug, there may be no market for it, even at a low price. The combination of limited ability to compel supply (through failure-to-supply clauses or contractual breach provisions) and low price responsiveness means that manufacturers face an asymmetry of incentives: there is little cost (except reputational) of producing too little of one drug (rather than another), but a potentially high cost of producing too much of that drug.

ASPE recently released a report on drug shortages that focused on sterile injectable cancer drugs, one of the classes of drugs where there are many shortages.[2] The market for sterile injectable cancer drugs is robust and growing. FDA analysis of IMS data shows that the number of vials of sterile injectable cancer drugs shipped between 2006 and 2010 increased by 14 percent, in part because of the aging of the population. Similarly, ASPE analysis of Medicare Part B data shows that between 2006 and 2011, the volume of services for sterile injectable cancer drugs increased by about 20 percent.

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[1] National Cancer Institute analysis of IMS National Sales Perspectives. In *Economic Analysis of the Causes of Drug Shortages*, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, October 2011, footnote 10.

[2] U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *Economic Analysis of the Causes of Drug Shortages*, October 2011. *http://aspe.hhs.gov/sp/reports/2011/drugshortages/ib.shtml*.

That increase in volume, however, did not occur across all sterile injectable cancer drugs. Using Part B data, ASPE compared the volume of services prior to shortages for sterile injectable cancer drugs that did and did not experience a shortage. On average, drugs that subsequently experienced a shortage are those in which the volume of sales was declining in the 2006–8 period prior to the shortages. Drugs that have not experienced a shortage since 2008 had an average 11 percent increase in volumes of services over this period, and a similar increase in the 2008–11 period that followed. The results suggest that manufacturers with limited capacity may be making strategic decisions about which drugs to produce when faced with falling demand for particular drugs.

THE CASE OF STERILE INJECTABLE CANCER DRUGS: CHANGES IN MARKET STRUCTURE AND PRODUCTION CAPACITY

Manufacturers can increase their portfolio of generic sterile injectable drugs by filing an abbreviated new drug application (ANDA) with the FDA, which must be approved before the manufacturer can market the generic drug. More ANDA approvals mean that manufacturers have more drugs to choose to manufacture with their existing capacity and therefore, manufacturers may substitute newer drugs for other drugs. Alternatively, they may increase the rate at which they make use of their existing manufacturing capacity. There was a substantial increase in the number of new injectable ANDA approvals beginning in 2008 (prior to the increase in sterile injectable drug shortages).

While the overall market for sterile injectable cancer drugs increased by 14 percent between 2006 and 2010, the number of vials sold by generic drug manufacturers increased much more rapidly—by nearly 30 percent. Over this period, the overall generic sterile injectable drug market (including cancer drugs and other classes of products) expanded by 52 percent. Some of this expansion was accompanied by reductions in brand manufacturers' production of these drugs.

Our analysis showed that generic manufacturers have expanded not only the volume of product they produce but also the range. In every year between 2006 and 2010, the number of new combinations in the market (a manufacturer producing a drug that it had not previously produced) exceeded the number of exits.

Expansion of the scope of production is also evident in the decisions of leading manufacturers to increase future manufacturing capacity. Several leading manufacturers of generic sterile injectable drugs indicated that they are upgrading existing facilities or building new facilities to serve this market. According to news reports and discussions with manufacturers, Hospira is investing $65 million in capital improvements in sterile injectable drug manufacturing sites, Teva is opening a new manufacturing site, and Ben Venue is opening a new, expanded facility to replace an older manufacturing facility.[3] These investments will increase capacity in both older and newer generic sterile injectable drugs.

Unfortunately, this new capacity is unlikely to come online for at least another 18 months. Meanwhile, when there is little excess manufacturing capacity, producing a new drug will often require manufacturers to reduce or stop production of another drug or to operate at a much higher than normal level of capacity utilization.

Increasing utilization of capacity is a good way of expanding supply in the short-run, but poses risks. High rates of capacity utilization may also limit the ability of manufacturers to perform routine maintenance and keep facilities in good order.[4] A recent report by FDA found that quality problems at drug manufacturing facilities resulting in disruptions in supply were the leading cause of drug shortages, accounting for 43 percent of all shortages.[5]

Supply Disruptions

The structure of the sterile injectable market, the recent expansion in volume and scope, and the consequent very high level of capacity utilization, mean that small disruptions to supply—such as may occur because of quality problems—which would otherwise be absorbed through diversion of capacity, can lead to cascading and persistent shortages.

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[3] News reports and personal communication with manufacturers. In *Economic Analysis of the Causes of Drug Shortages,* U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, October 2011, footnotes 16–17.

[4] Donald Gross, John F. Shortle, James M. Thompson, and Carl M. Harris, *Fundamentals of Queuing Theory*, Fourth Edition, John Wiley & Sons, Inc., Hoboken, NJ, 2008.

[5] U.S. Food and Drug Administration, *A Review of FDA's Approach to Medical Product Shortages*, October 2011. *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm*.

Over time, entry and expansions in capacity in the industry, should lead to a situation where shortages due to supply disruptions are sporadic and rare. In the current environment, where capacity is severely constrained, shortages induced by disruptions can cascade throughout the sector and persist for long periods of time.

RECOMMENDATIONS

The Administration is doing everything in its power to address the shortages administratively. There a few areas where additional authority or action by Congress may be needed or where the private sector can take steps. Based on our examination of the underlying factors that lead to periods of shortage in the prescription drug market, and particularly the underlying market factors that have contributed to the current shortages in the area of sterile injectable drugs, we offer a few recommendations.

Policymakers must balance the short-run benefits of tailoring regulatory responses to specific situations against the risk of strategic behavior and consequent reductions in competition in the long run.

Steps that both expedite expansion of supply and maintain product quality in sectors with high capacity utilization could reduce the risk of shortages not only in the current situation, but in the future as well. To facilitate this, FDA can expedite review of new manufacturing capacity in this area, and we understand that FDA is already doing this and committed to continuing to do so.

Private organizations that purchase drugs (including GPOs), can help to alleviate future shortages by negotiating with drug manufacturers to strengthen the failure-to-supply requirements in their contracts. Such contractual changes are likely to incentivize drug manufacturers to invest in extra capacity of both production lines and active pharmaceutical ingredients.

As part of the Administration's broader effort to work with manufacturers, health care providers, and other stakeholders to prevent drug shortages, the President has directed the FDA to take steps that will help to prevent and reduce current and future disruptions in the supply of lifesaving medicines and FDA is responding to this directive.

The Administration also announced on October 31, 2011, its support for bipartisan legislation (S. 296 and H.R. 2245) that would require all prescription drug shortages to be reported to FDA and would give FDA new authority to enforce these requirements.

SUMMARY

In summary, the current class-wide shortages in the sterile injectable drug industry appear to be a consequence of a substantial expansion in the scope and volume of products produced by the industry that has occurred over a short period of time, without a corresponding expansion in manufacturing capacity. The current shortages will likely be resolved when new supply sources come online as the manufacturing industry increases its capacity. In the meantime, the FDA's Drug Shortage Program is working diligently with manufacturers and other stakeholders to mitigate the effects of the shortages and the Administration is doing everything in its power to address shortages administratively.

I appreciate the opportunity to speak with you about our analysis of drug shortages. I would be happy to respond to any questions.

The CHAIRMAN. Dr. Glied, thank you very much.

Dr. Kweder.

STATEMENT OF SANDRA KWEDER, M.D., DEPUTY DIRECTOR, OFFICE OF NEW DRUGS, FDA, WASHINGTON, DC

Dr. KWEDER. Good morning, Mr. Chairman and members of the committee. Thank you, thank you, thank you for holding this hearing. I am Dr. Sandra Kweder, as introduced. I'm the Deputy Director in the Office of New Drugs in FDA.

This problem of drug shortages is a very serious problem for patients, and it's a serious problem for medical care providers in this country, and I think it touches every one of us or our families in some way.

My colleagues and I, at FDA, take this problem very seriously, and we look forward to continuing to work with you and our other colleagues in the profession to find short- and long-term solutions.

Today I want to highlight FDA's ongoing actions to prevent and mitigate shortages, as well as mention some more recent efforts by the Administration to address this problem.

You already stated that the number of drug shortages has been rising steadily over the past 5 years, to a level that we would never have anticipated. In 2005, we reported a total of 61 actual drug shortages for that year. By 2010, the number was 178 in that year. That rising trend has continued into 2011. Between January and October of this year, we were tracking 220 actual shortages. That doesn't include the ones that we prevented.

In July of this year, Dr. Howard Koh, the Assistant Secretary of Health at HHS, started to convene a series of meetings with representatives from across the Department, including us and Dr. Glied, to try and understand more about the roots of drug shortages and what we could do with our existing authorities to decrease their frequency.

In September, we at FDA held a public meeting to try and gain additional insights into the causes and impacts of drug shortages, and some possible strategies for preventing or mitigating them. We were open to any ideas that we hadn't already thought of. The insights that we gained from that meeting on the effects of this problem on patient care and patients were staggering.

On October 31 of this year, the Administration took a series of steps to reduce drug shortages, including issuance of an Executive order by the President, an announcement of support for bipartisan legislation, and FDA directly communicating with manufacturers to encourage them to voluntarily continue to report any problems that they were having that might ultimately result in a drug shortage.

That Executive order had three main components. One was directing FDA to use all appropriate administrative tools to require manufacturers to provide us advance notice of shortages. It directed us to continue to expand our efforts to expedite our work in reviewing manufacturing applications and conducting inspections where needed, and to work with the Department of Justice to examine whether secondary wholesalers or other market participants were responding inappropriately or illegally by creating a gray market with price gouging.

In parallel, a number of things occurred. HHS released two reports, one by Dr. Glied and her colleague, and one by FDA to report on our views on the current status of medical product shortages and the agency's role in monitoring, preventing, and mitigating them. That same day, we in FDA sent a letter to every single pharmaceutical manufacturer reminding them of what their legal obligations were to report to us under very narrow circumstances about discontinuing product production, but also urging them to notify us early when they had any problem that might result in a drug shortage.

Since that time, we at FDA have been continuing to tackle the problem of drug shortages head on. There is no question that we have our work cut out for us, but this is a public health crisis, and we're responding. We have always had strong internal working re-

lationships in the agency on these matters, and we are continuing to expand our efforts to communicate with the industry in this work.

Since October 31, there has been a significant increase in notifications about the number of potential shortages to us. Our efforts are having an effect. We used to get about 10 notifications a month of a potential shortage. Since October 31, we have had 61 notifications, a sixfold increase. They continue to identify areas where we can help, and we have helped in many of those cases. But they also continue to show us serious quality-related problems that firms are having in production of quality drug products.

Nonetheless, as a result of these reports, we've intervened to prevent 96 drug shortages. Now, in one intervention alone, we prevented 86 shortages at a single plant. We're working to resolve quality problems with firms and review and expedite applications that they have in place that would mitigate any potential shortage. We have doubled the number of our staff in the drug shortage program. We have drafted guidance for industry on what exactly we think is helpful for them to report and under what circumstances, and just today we've published an interim final rule that clarifies and expands some of the definitions within our legal authority to require reporting for product disruptions where a company is the sole source provider of an important drug.

Since October 31, we've been engaging in a series of meetings with stakeholders, including individual companies, industry organizations, medical care providers, Pharma and bio and other organizations who are interested in finding solutions to this problem. One of our most important goals we have for these meetings is finding ways to facilitate industry commitment and performance in producing high-quality products.

On a separate track, I want to mention something critical. Many characterize FDA's activities in this area in working with companies as going in with an inspection, walking out the door, and leaving the company a list of deficiencies and telling them they need to shut down overnight. Nothing could be further from the truth.

These companies are usually long aware of the problems that they have had. We have cited them a number of times, and we continue to meet regularly with firms that are having difficulty maintaining quality manufacturing. We are also beginning the process of improving our new drug shortage database for internal tracking of shortages, as well as utilizing the database to develop better prediction models for who might be at risk.

And finally, we've initiated communication with the Department of Justice as directed in the Executive order about how to share information that we receive about price gouging out in the community, and we understand that the Department of Justice is also reaching out to the National Association of Attorneys General to understand whether there are State and local laws that can help address some of these problems.

Overall, our goal is to ensure that we and all of our stakeholders share and act on the same commitment to high-quality drugs that the American public can continue to rely on when they need them.

I look forward to working with you, and I am happy to answer questions.

[The prepared statement of Dr. Kweder follows:]

PREPARED STATEMENT OF SANDRA KWEDER, M.D.

INTRODUCTION

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

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

Background

FDA defines a drug shortage [1] as a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level. The impact of drug shortages on patients can be significant and even life-threatening. Certain drugs that recently have been in shortage—such as "crash cart" drugs—can literally be lifesaving in the acute setting, while others, such as outpatient chemotherapy drugs, must be administered within days or weeks to provide maximum benefit. Shortages of these drugs not only have an impact on clinical decisionmaking, but they could also significantly affect patient outcomes. For example, a shortage of propofol, which is used as a sedative and for general anesthesia, led clinicians to substitute etomidate, resulting in eight suspected cases of phlebitis (inflammation in a vein) in a single hospital system. Other drugs that have experienced shortages, such as the cancer drug cytarabine, arc important drugs not only because they treat a critical disease, but also because they lack an effective alternative.

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

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

The number of drug shortages has been rising steadily over the last 5 years. In 2005, CDER reported a total of 61 shortages; by 2010, that number had risen to 178.[2] The rising trend of drug shortages has continued into 2011, with 220 shortages tracked by FDA from January through October of this year. Although shortages can occur with any drug, shortages of sterile injectables currently make up a large and increasing share of these shortages, despite the fact that sterile injectable drugs comprise a small percentage of the overall prescription drug market. These include critical products such as oncology drugs, anesthetics, parenteral (intravenous) nutrition drugs, and many drugs used in emergency rooms.

Of the 127 drug shortages tracked by FDA during the period from January 1, 2010, to August 26, 2011, oncology drugs accounted for 28 percent of shortages, followed by antibiotics at 13 percent. One hundred eighteen shortages (93 percent) involved medically necessary drugs and 52 of the shortages (41 percent) were both medically necessary and sole-source drugs.[3] For the purpose of prioritizing our work to address shortages, we consider a drug medically necessary if it is used to prevent

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

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

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

or treat a serious or life-threatening disease or medical condition for which no acceptable alternative drug is available.

Reasons for Drug Shortages

There is no single reason that drug shortages occur. The Agency has identified a variety of root causes of drug shortages, some of which I will discuss here. Ultimately, in any given drug shortage, many factors are involved, and underlying causes may operate alone or in combination to result in an individual shortage. These include, but are not limited to, industry consolidation, shortages of underlying raw materials, inventory and distribution practices, difficulty in producing a given drug (e.g., sterile injectables, which entail a much more complex manufacturing process than solid dosage forms), quality and manufacturing problems, production delays, discontinuations for business reasons, and unanticipated increases in demand.

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

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

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

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

Actions to Prevent or Mitigate Shortages

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

When FDA becomes aware of a potential drug shortage, either from pharmacists, physicians, pharmacy organizations, manufacturers or other sources, the Agency works collaboratively with the affected firm or firms to return the product to its usual market availability as quickly and as safely as possible, while helping prevent any harm to patients. Although FDA cannot require firms to continue production

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[4] Unapproved drugs are drugs that have not received FDA approval to be legally marketed.

[5] "A Review of FDA's Approach to Medical Product Shortages Drug Shortage Report". *http://www.fda.gov/AboutFDA/ReportsManualForms/Reports/ucm275052.htm*.

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

of a product or increase production in response to a shortage, it does encourage other firms that make the drug to ramp up production, if they are willing and able to do so. FDA also expedites the review of submissions from manufacturers that may alleviate the drug shortage, which may include requests from existing manufacturers to extend the expiration date of products, make manufacturing changes to increase capacity, use a new raw material source, or change product specifications, as well as applications from new manufacturers who may be willing to enter the market to address a shortage situation. When a shortage is caused by manufacturing and quality problems, FDA works directly with the affected firm to develop short- and long-term solutions to the problems. FDA can also use its regulatory discretion for a manufacturer to continue marketing a medically necessary drug, if the manufacturer can develop a method to resolve a quality issue prior to the drug's administration.

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

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

FDA can also use its regulatory discretion with regard to the temporary import of non-FDAapproved versions of critical drugs, when a shortage cannot be resolved immediately. However, there are several factors that limit the applicability of this option. The product may already be in shortage abroad, which may hamper our ability to alleviate the problem in the United States. In addition, although there may be foreign suppliers that possess or have access to a particular drug, these suppliers are not necessarily FDA-approved and may need to be inspected, and their drug labels evaluated, before a product can be imported into the United States. Once a foreign firm is identified as willing and able to supply the drug, FDA can exercise enforcement discretion for the temporary import of a foreign drug after ensuring there are no significant safety or efficacy risks for U.S. patients. The temporary importation is tightly controlled and distribution is closely monitored. For example, FDA must ensure that drugs imported from abroad are manufactured in a facility that meets FDA quality standards. FDA will then post information about the imported drug on the drug shortage Web site.[7] FDA has done this for the import of a number of critical drugs during a shortage, including: propofol, Foscarnet, ethiodol, thiotepa, norepinephrine, Xeloda, leucovorin and levoleucovorin.

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

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

as a result of voluntary notification and close collaboration with manufacturers to avert shortage situations.

Recent Efforts to Further Reduce and Prevent Drug Shortages

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

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

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

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

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

In addition, FDA sent a letter to pharmaceutical manufacturers,[12] reminding them of their current legal obligations to report certain discontinuances to the Agency, and urging them to voluntarily notify FDA of all potential disruptions of the prescription drug supply to the U.S. market, even where disclosure is not currently required by law. The letters to manufacturers and the Executive order have produced a significant increase in the number of potential shortages reported to FDA. In the 10 months preceding the Administration's actions (January through October 2011), the Agency received an average of approximately 10 notifications per month. In the 4 weeks following the letters to the manufacturers and issuance of the Executive order, we received 61 notifications, a sixfold increase.

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

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[8] "Drug Shortage Docket Web site: *http://://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0690-0001.*

[9] *http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages.*

[10] Press Release: *http://www.whitehouse.gov/the-press-office/2011/10/31/we-can-t-wait-obama-administration-takes-action-reduce-prescription-drug.*

[11] *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm.*

[12] *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm277675.htm.*

• Doubling the number of staff in the Center to assist in coordination and response activities, as well as expediting actions (e.g., inspections) that would help to alleviate drug shortages;
• Developing several guidances for industry on reporting product disruptions, supply interruptions, and potential shortages;
• Meeting with various stakeholders to discuss shared opportunities to prevent and mitigate shortages, including; the Generic Pharmaceutical Association, the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization and drug wholesalers;
• Exploring options for improving the drug shortage database for the internal tracking of shortages, as well as utilizing the database to develop prediction models for drug shortages;
• Assessing commercial systems that could be contracted to provide ongoing or periodic data on sales and distribution of drugs at the wholesale level to detect early signals of potential shortages or supply disruptions;
• Working with the Department of Justice, as directed in the Executive order, regarding issues related to price gouging and hoarding, including reports from pharmacists and other health care providers in connection with drug shortages;
• Announcing a public meeting on proposed recommendations for establishing a generic drug user fee. The primary goal of this user fee program is to bring median time to approval from around 30 months to a primary review goal of 10 months. This will bring generics to market faster, which should help alleviate shortages. In addition, FDA will continue to prioritize review of generic applications for products that are in shortage situations.

CONCLUSION

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

The CHAIRMAN. Thank you both very much. We'll start a round of 5-minute questions.

Dr. Glied, reading your testimony last night, what caught my eye was this paragraph. You said,

> "It's important to note that the low price responsiveness of demand for sterile injectable drugs also has implications for inventories and capacity decisions. If there is an excess supply of a particular drug, there may be no market for it, even at low prices."

And you say,

> "The combination of limited ability to compel supply through failure-to-supply clauses or contractual breach provisions and low price responsiveness means that manufacturers face a symmetry of incentives. There is little cost of producing too little of one drug, but a potentially high cost of producing too much of that drug."

OK. How do you solve that conundrum?

Ms. GLIED. It's a challenging problem because I think one of the things we need to think about here is how—one of the things that we raise in the paper that we wrote is how to think about the private market responding to a lot of this change, because if we think about this sector, it's really mostly a private market issue. The

group purchasing organizations are private, and the drug manufacturing firms are private also.

So one of the things that the economists we spoke with suggested to us is that some of this could happen through the contracting processes that exist between the group purchasing organizations and the manufacturers, trying to essentially have the group purchasing organizations put more of a premium on having the supply in hand, not just getting the lowest price but making sure that the manufacturer really actually has that supply available.

That's something that's got to work itself out in the market, because right now the real challenge is if you're a manufacturer, you want to produce just the right amount for the market, and in the cases where there's only a sole source manufacturer, that's not such a complicated problem. You know what the market is, you can produce it. But when there are two or three different companies producing the same drug, and that's typical for this generic kind of industry, you're not only thinking about how much you produce, you also have to think about how much your competitors are likely to produce, and you can create real instability in the market as those things turn around.

The CHAIRMAN. Then your report discusses how better "failure supply clauses" in these group GPO contracts could help mitigate the drug shortage crisis. Can you elaborate on that?

Ms. GLIED. One of the things that we learned in talking to group purchasing organizations and manufacturers is that most group purchasing organization contracts do include a clause in them that says that if a manufacturer is unable to produce a drug that they were contracted to supply, they have to pay the difference between the cost of the drug at the price that they contracted for and the price at which somebody can buy the drug.

Unfortunately, what happens is that when a drug goes into shortage and you can't buy the drug at any price, those contracts become moot, they don't hold any force anymore. So we thought that one of the things that might happen here is that private sector manufacturers might work with those contract terms to try and make them work so that even in the case of a supply shortage, you would push a little bit more of that responsibility to the manufacturers.

The CHAIRMAN. Dr. Kweder, again looking at your testimony, one thing that caught my eye last night in reading this is that FDA does not have the statutory authority to require firms to continue production if they decide to stop, or require other firms to increase production in response to a shortage. Firms are statutorily required to provide FDA with notice of manufacturing discontinuations only in limited circumstances, and FDA lacks explicit authority to impose penalties on firms that do not submit required reports of discontinuations.

How important an aspect to this shortage problem is that?

Dr. KWEDER. We think it's extremely important. The root of them from our window is—we don't get into the finances—is when a company is having problems producing a quality product, they're having trouble in a plant, they do not—until there is a crisis—they typically do not come to FDA and say we're having a problem here, we need your help, we think we're going to have a problem pro-

ducing a product. It's not our job to go to our competitors and ask them to ramp up production of a critical product, but we need some help.

If we know about that, we can do that.

The CHAIRMAN. My time is running out. One last thing. So if you've got two, three or four manufacturers and if they each supplied you with this information, then you would be able to tell whether or not we're facing a shortage from one day to the other.

Dr. KWEDER. That's right. That's exactly right.

The CHAIRMAN. Thank you very much.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

Dr. Glied, the president of the Generic Drug Manufacturers Association, Mr. Ralph Neas, has told the committee that drug pricing issues are not the cause of the current drug shortages. Do you agree with Mr. Neas and the Generic Drug Manufacturers that pricing is not the cause of the current shortages?

Ms. GLIED. Yes, sir. I agree.

Senator ENZI. Thank you.

Dr. Kweder, how many supplemental and new generic applications are in the current backlog that could help mitigate a shortage if they were approved? Is FDA prioritizing or expediting these applications for review?

Dr. KWEDER. The answer to the second question is absolutely, yes. We do have a longstanding backlog of generic drug applications, but it's important to look at what those applications are, and they can be for things like a new application, a new drug producer, they can be for a new source of an ingredient, or for a manufacturing change.

We do monitor that queue and are well aware of the ones that—as we hear about potential drug shortages, we are constantly looking at that queue to pull things out that might expedite them in order to prevent a drug shortage, which is one of the reasons that early notification of a potential problem is so important. That's exactly what we can do.

Senator ENZI. Thank you. I've also heard about the amount of time that it takes for different stakeholders, ranging from 6 months to 3 to 4 years for approval. How long does it take to get FDA approval to a manufacturing facility change? Can you give some specific examples where the FDA has met the 6-month goal?

Dr. KWEDER. A lot of that depends on the facility or where the facility is. In many cases, companies are coming to us seeking to change facilities, and it's a facility that we know well. It's moving to another plant. Those can be turned around very, very quickly. If it's a facility in another country, for example, that we're familiar with, we often have a great deal of information about that facility, or if we don't, our international colleagues—who we have cooperative agreements with and understandings with—may have already inspected those facilities and be quite familiar with them, and share that information with us so that we can expedite action on that particular facility.

There is a big difference in how we do business when we think there may be a critical product, a highly medically necessary prod-

uct with a potential for supply, we can expedite those and meet those goals, and we do.

Senator ENZI. Thank you. I was very impressed with your information about what's happened since October 31, when the President did his Executive order, and I won't ask you to provide it right now. If you can provide us with a list of the specific drug shortages that were prevented and how you did it, that might be helpful as we're doing the legislation as well.

Dr. KWEDER. We can do that.

Senator ENZI. OK, thank you. And can you tell us how the Office of Generic Drugs coordinates with your office when evaluating applications for the manufacturing upgrades, active pharmaceutical ingredient approval, or drug applications?

Dr. KWEDER. Our office and the Drug Shortages Program work very closely. In effect, we have key contacts and kind of a SWAT team approach that's ongoing with the Office of Generic Drugs and our Office of Compliance, and the Office of New Drug Chemistry, all scientists who are involved in the actual review of the applications. So we coordinate very closely. We are in contact with them on a daily basis sharing information about what we're hearing, what applications they have, the status of those applications, and also ongoing interactions with anyone such as our inspectors in the field who may be going into any of those plants and working with companies to address problems. It's a daily contact.

Senator ENZI. Thank you. I'll yield the balance of my time.

The CHAIRMAN. Thank you, Senator Enzi.

I have an order of appearance here: Senator Kirk, Senators Franken, Merkley, Isakson, Bennet, Bingaman, Whitehouse, Blumenthal, Casey and Hatch.

Senator Kirk.

Senator KIRK. I thought your testimony was outstanding in describing the problem. Dr. Kweder, I asked Shauna to prepare me for this hearing. I wanted to drill into one patient and one therapy in which we were in shortage. It's non-Hodgkin's lymphoma, and the shortage of doxorubicin. And the story of the shortage for non-Hodgkin's lymphoma patients I think is instructive of the problem here. It's supplied by three companies, and according to the briefing I got, doxorubicin shortage is due in part to one of the four companies that makes the drug, Teva Pharmaceuticals, was told earlier this year to stop manufacturing the drug by FDA.

Meanwhile, demand for the drug has increased according to the American Society of Health System Pharmacists, and another supplier, according to ABC Bedford Laboratories, say they're currently facing a manufacturing and capacity constraint.

So we have, I think, problems that we can solve and problems that we can't solve. If an individual private supplier is having difficulty or is deciding to get in or get out of business, I think it's a nonstarter for the Congress to order a private concern to produce a pharmaceutical which it does not want to produce. We should not get into that game.

But with regard to the Teva Pharmaceuticals question where the FDA is ordering them to stop and then triggering a shortage, I agree with Senator Blumenthal that the Klobuchar legislation is good, but I would argue to go one step further. I very much appre-

ciate the work that your office has done, and I think you are a very effective advocate inside FDA, but I would like you to have increased powers.

My hope is that this committee could consider something like providing the Center for Drug Evaluation and Research a new authority that I would call, for lack of a better term, a patient care balancing authority, so that if we find a shortage which, in your testimony, was very good. You say total supply of the clinically interchangeable version of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level, that you then have a patient care balancing authority to take action within FDA to remedy the situation within 6 months.

And I would argue that we should then go further and say if you find that the drug is vital to the survival of a patient which, for example, in oncology that would be the case, that your patient care balancing authority would be able to remove FDA barriers to supply within 1 month, and I don't think you would actually have to use this authority that much.

But the fact that we have given you this authority would then give you so much greater weight inside the bureaucracy, because we make many decisions inside FDA to stop or halt or suspend, but if the decision is for patient death, we definitely need the Dr. Kweder operation, the CDER office to have greater authority, and I would call that a patient care balancing authority. But if you could comment?

Dr. KWEDER. First I want to correct something. FDA did not tell Teva that they had to stop producing.

Senator KIRK. Oh, OK.

Dr. KWEDER. OK? And I think that's important. We had been working with Teva for quite some time on really major quality production problems. This was not a new situation. This was ongoing.

They ultimately made the decision that the only way that they could correct it was if they shut down, and I can't comment on the specifics of whether that was entirely necessary. That's not within my purview today.

I think the problem that ultimately resulted because, as you said, there were other companies producing it, is really illustrative of Dr. Glied's testimony and findings, that while there are other companies that produce it, they cannot—because of their production model, their 24/7 model—they cannot turn on a dime and ramp up production to meet a need when Teva makes a legitimate or not legitimate decision about what they need to do.

I don't think that additional FDA authority, as much as I welcome additional authority, would necessarily fix that problem. I am happy to tell you that Teva is coming back online in producing doxorubicin, if it's not available already, and we recently approved yet another supplier. Pfizer, not typically a generic producer, has stepped in and started to produce that drug to help make up that shortfall. That will help hundreds of thousands of cancer patients. It's a success story.

Senator KIRK. If I could just finish up, I just hope, though, that in your testimony you said we have a growing shortage problem, which means for whatever reason, patients are being disadvantaged.

Dr. KWEDER. That's right.

Senator KIRK. And I'm particularly worried about their lives being lost. As Senator Franken said, if we switch from doxo to the other alternative, we just dropped the patient survival rate by two-thirds, and I would like you to have greater authority inside FDA to make that argument.

Dr. KWEDER. We'll be happy to work with you on that. Thank you.

Senator KIRK. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Kirk.

I have to excuse myself from presiding. Senator Enzi will preside in my absence.

And next is Senator Franken.

Senator FRANKEN. Thank you, Mr. Chairman.

I want to thank you both for your testimony.

Dr. Kweder, in her written testimony, Dr. Glied said that 43 percent of all shortages were caused by quality problems at drug manufacturing facilities. I've also heard that when some manufacturers have compliance problems with the FDA's good manufacturing practices, they take their product off the market rather than investing money to fix the problem.

What could FDA do to help maintain the quality of drug lines while at the same time avoiding unnecessary shortages? And how often does FDA's compliance office coordinate with the drug shortages office so as to make sure that their actions do not precipitate a shortage?

Dr. KWEDER. Let me answer the last question first. We coordinate regularly with our Office of Compliance and our Office of Regulatory Affairs that is out in the field conducting inspections. In fact, we recently have changed our practice to require that before our district office people issue a letter or our Office of Compliance issues a warning letter, that they specifically address how any of the actions, any actions proposed might result in a drug shortage, take that into consideration.

We do it already, but this sort of cements that process and assures it.

The kinds of quality problems that are occurring in these plants, these are not people not crossing T's and dotting I's. The key to producing a quality product for particularly these injectable drugs is that they have to be produced under very tightly controlled circumstances. I don't know how many of you have ever been in one of these plants. If you're a woman, you're not allowed to wear nail polish in the plant, something that would seem to be quite permanent, because there's a risk that if it gets into the air or into the system, it could contaminate a product that would be injected into a cancer patient's veins. So maintaining quality is really the company's job.

The standards are very straightforward. They are the same and have been, but modernized, current. They've been the same for a long time. And counter to what some would say, they are highly consistent across most Western nations. Our standards, the European Union standards, Australia, and Canada, are highly consistent and similar.

We do work with companies. The first time we do an inspection and find a problem, we monitor them. We go back. We check on their progress. We require that they report to us what they are doing to address it. Oftentimes when we go back in and re-inspect, we find that none of those things have been done. So we go back through this again.

Most companies do an outstanding job. But there are some that don't, and unfortunately some of the ones that are under the most production pressure are making the most drugs. These companies that are at the root of most of these shortages, Dr. Glied pointed out, make hundreds of products, hundreds. There is no cushion there for them to shut down a little bit to fix a problem or shut down temporarily.

Senator FRANKEN. Dr. Glied, according to a report your office released in October, about half the shortages, at least until 2010, were for oral medicines like tablets and capsules, not for injectable drugs. But for 2010, 74 percent of shortages involved sterile injectable drugs like anesthetics and chemotherapies.

What brought about the sudden shortage of generic injectable drugs? And several proposals to address this problem have included changes to the physician reimbursement for these drugs. Are we really going to solve this by changing how we pay for health providers for drugs in shortage?

Ms. GLIED. Let me start with your second question, which is the easier one. As I think we pointed out, there's a quite rigid disconnect between the price that health providers are paid, the fee that they're paid to compensate for the cost of procuring drugs, and the price that manufacturers are paid by group purchasing organizations for those same drugs. In some cases, for example, when drugs are used under the Medicare Part A program, there's actually no fee paid in direct compensation to the provider at all, but the price that a manufacturer gets is based on a negotiation between a group purchasing organization and that manufacturer that encompasses all the drugs the provider uses regardless of who the payer is, whether it's private insurance or Medicare Part A or Medicare Part B.

There's a really rigid disconnect there, and that's why I think we believe that changing the prices that are paid to health care providers would have no impact on the amount of money received by manufacturers in this sector.

As to your first question, I think the problem is multifactorial, but one thing that we saw in the data that we looked at is that there has been a big increase in the volume and number of drugs available to generic manufacturers over this period, I think a very healthy increase that mainly came about because a lot of branded products went off patent. So the potential market for the generic manufacturers grew. At the same time the population is aging, and these sterile injectable drugs, that market is really growing very robustly.

In the beginning, what that led these manufacturers to do is to increase their capacity utilization, and our hypothesis is that that increase in capacity utilization just led to more of the kinds of quality problems that Dr. Kweder has pointed out. Then you start having this cascading effect, because there are not that many manufac-

turers, not that many plants in this business. Once one of them goes offline because they're having a quality problem, it just cascades through the industry, and that's why we anticipate that it won't be until the new manufacturing capacity, which is in the works, really comes online that this problem is going to solve itself, and until then we really will need the FDA to keep managing it.

Dr. KWEDER. And I would add that we are working with those companies right now, as they are making plans for their new plants and trying to build quality in.

Senator FRANKEN. Thank you.

Senator ENZI [presiding]. Senator Merkley, and then Senator Isakson.

Senator MERKLEY. Thank you very much, Mr. Chair.

I wanted to start simply by noting that the GAO report goes through a host of different strategies that FDA uses, eight different strategies, and that they fall largely into helping with manufacturing problems, helping with importation, and then flexibility in terms of allowing a drug to be marketed that maybe doesn't have the right labeling or right quality.

It just strikes me as fascinating that a for-profit company is running into a manufacturing problem and FDA is able to help them resolve that problem. I don't quite understand. Can you explain to me how it is that these experts in manufacturing need your help to figure out how to solve a manufacturing problem?

Dr. KWEDER. I think that's a good question, and we struggle with that to some degree ourselves. One of the reasons that FDA can sometimes get involved is we see all of the companies. We see where they've been. We have a broader view of manufacturing processes than sometimes an individual company might. We also are able to work with them to help them identify new strategies because we've seen other companies use particular strategies.

But as to the broader question about why they would come to FDA for advice, why they would need FDA's advice in the first place, I'm not sure that I have an answer for that. What we can do, though, is that we can help them prioritize by taking into account things like products that we think may be medically necessary or highly critical for patient care, and help them prioritize potentially a panoply of problems that they're trying to address at once.

Senator MERKLEY. Let me move on. I'll leave that as a bit of a mystery for now.

But neither of you has really gotten into this question that we keep hearing about, about the gray market, about groups that are following the drug market well enough to realize there's going to be a shortage and knowing that, basically corner the market on that drug, buy up the surpluses and accentuate the shortage, the scalping problem. And the fact that it hasn't featured prominently in either of your testimony is interesting to me because it's often put forward as part of why there's been such a dramatic change over a 2-year period.

Is drug scalping a significant part of this problem?

Ms. GLIED. I think that what we would say is that the gray market is a symptom of the problem. I mean, it is a problem in itself, but it arises because of the underlying problem of shortages. If the

problem of shortages weren't there, the gray market would not be able to exist and survive. Addressing the gray market is important because price gouging is a significant issue, but addressing the gray market by itself is, unfortunately, not going to solve the whole shortage problem.

Dr. KWEDER. And I would add that we don't actually have a lot of information about what's called the gray market. We get reports from pharmacists or health care providers or health systems about experiences they've had and what kinds of prices that they're paying, but this isn't an area where FDA has any authority, and it's one of the reasons that we are beginning to work with the Department of Justice, and we'll also have to work with the Federal Trade Commission, to try and understand this a little better and see what we can do.

From our standpoint at FDA, some of the gray market activities are a signal to us to be aware that there may be counterfeit products involved, another challenge that we have in this country. It's a signal to us to begin to go into that zone and start to assess whether there may be counterfeit products at play.

Senator MERKLEY. I'm running out of time, so I'll just note that I want to explore this more, because just as we see with tickets for a sporting event, if there is a high demand and low supply, scalping is far more effective, but the scalping accentuates the problem. And the fact that neither of you has a firm grip on the role it's playing says we really need to dig into this piece, because in many markets there's a response. The response is it's illegal to sell beyond the face value of the product. That can take the heart out of scalping overnight. I want to find out, is that something we need to do in this area?

Thank you, Mr. Chair.

Senator ENZI. Senator Isakson, and then Senator Bennet.

Senator ISAKSON. Thank you, Mr. Chairman.

Dr. Kweder, when you were responding to Senator Merkley's question regarding a pharmaceutical company coming in to you seeking advice when they've got a manufacturing problem, wasn't that the question? It would seem to me that would be logical. If I was producing a product and I was regulated by a government entity and I had competitors, I'd sure come to the Government rather than the competitor to give me advice, because all I'm doing is telling them I've got a problem. Am I right?

Dr. KWEDER. I think so.

Senator ISAKSON. And does the FDA try and be a problem solver when a manufacturer comes to them and give them recommendations that they might have missed otherwise?

Dr. KWEDER. We consider our job to be problem solvers, and our job is to facilitate, help facilitate these companies being able to make a high-quality product. That is at the core of what we do.

Senator ISAKSON. You said in your testimony that you prevented 96 shortages I think this year or last year.

Dr. KWEDER. Actually, that's just since October 31.

Senator ISAKSON. Please tell us. I want to followup on Mike's question. How did you do that? That seems like why we're having the hearing, so I'd like to hear that.

Dr. KWEDER. Yes. In a lot of those cases what we have done, is worked with manufacturers to help them get certified additional supplies of critical ingredients, to help them bring a new production line on board, to make changes in their manufacturing process, or to help solve quality problems, help them find creative approaches to quality problems. They may be thinking about an approach and aren't sure about it. They'll come to us, and we'll have a conversation about what makes the most sense and what's the most pragmatic.

Other things that we have done to prevent these shortages are, we have gone to competitors of these firms and encouraged them to ramp up production, thereby putting more in place on the market so if a company having a problem feels like they have to go offline, there will be supply available. In some cases we have gone to sources that are outside this country to help find alternative supplies.

Those are just some examples. In other cases where there have been problems, where the company may be having a systemic problem on multiple lines and we think that one production line could be protected with additional controls to ensure quality, we have helped them continue making a product while other things around it were not able to be made.

Finally, we have done some very creative things where, in response to one shortage, one company ramped up production and found that the stress of increasing production was leading to them having precipitate in their injectable drug. You looked at it and it was cloudy. Well, we worked with them to figure out that if you just warmed the vials, the precipitate would dissolve. What they were able to do was label the drug with that, send it packaged tightly with instructions and notify hospital pharmacies that would be administering it that that was the way to do it, rather than have to not ship the product.

Those are some examples.

Senator ISAKSON. Dr. Glied, I'm not a doctor, I'm not a pharmacist, I'm not scientifically inclined, so I may say something stupid right here, but the growth in cancer drugs in particular, but a lot of drugs, are biologics. When you talk about a sterile injectable, is that talking about a biologic?

Ms. GLIED. It could be a biologic. I don't think most of these are biologics.

Senator ISAKSON. Then my question——

Ms. GLIED. I'm not a doctor either, so I have to confess.

Senator ISAKSON. OK, that makes two of us. With the growth of biologics, have the shortages become disproportionately biologic-based drugs, or chemical compound drugs?

Dr. KWEDER. To date, the answer is no, but biologics do offer really special and challenging problems because there are not generic biologics, and they tend to be made by one company. Now, the good news about that is that companies guard their biologic production and monitor it very, very closely. But there is always the risk of unanticipated problems.

We have had some of those. But the majority of the shortages, the vast majority, have been for nonbiologics or small-molecule drugs.

Senator ISAKSON. OK. Thank you, Mr. Chairman.

Senator ENZI. Senator Bennet, and then Senator Bingaman if he returns. Otherwise, Senator Whitehouse.

Senator BENNET. Thank you. Thank you very much, Senator Enzi. And thank you for your testimony, both of you.

Dr. Kweder, as you know, our country does not have a nationwide drug distribution system to know where drugs are across the supply chain from manufacturers to patients, and as a result, when hospitals and pharmacies are approached by distributors who may actually have an additional supply of pharmaceutical drug that may be in shortage, the hospitals and pharmacies can't always verify the legitimacy of that drug. And even in this time of fiscal constraint, that's why I'm supportive of a drug distribution system that does—while it doesn't create unduly burdensome costs for any part of the supply chain, it would provide us knowledge about where drugs are in the system, and I wondered whether you'd think it would be helpful for the FDA and other supply chain stakeholders to have information on the legitimacy and pedigree of a drug, particularly when a drug is in shortage.

Dr. KWEDER. Yes. I think that it won't solve a drug shortage problem, but it would allow hospitals, pharmacies, and the agency to have a better idea of whether a product is a legitimate product. I already mentioned that one of the concerns that we have about the gray market is whether some of these are actually signals of counterfeit, and that would make assessing that very much more straightforward.

Senator BENNET. And it's my point of view, I don't know whether you would agree, but that there are a lot of reasons why we would want to be able to track pharmaceuticals across the country, but those reasons are particularly in stark relief when you think about the shortage issues. We'll look forward to working with you on that.

Dr. KWEDER. Thank you.

Senator BENNET. I had a second question for you, as well. You mentioned in your testimony that FDA can use its regulatory discretion for temporary importation of nonFDA-approved versions of critical drugs when a shortage can't be resolved immediately, and you've noted that there may be foreign suppliers—you were just talking about this with Senator Isakson—that possess or have access to a critical drug but are not FDA-approved and may need to be inspected.

At an earlier hearing on the safety of our drug supply, GAO reported that at FDA's current pace, all establishments abroad could be as long as 9 years from now. I wonder whether you think that FDA's desire to better use third-party resources and to use inspection information from other top-tier countries to maximize resources will have a positive effect on reducing drug shortages.

Dr. KWEDER. I think it already is having a positive effect on reducing drug shortages. We get a great deal of information from our regulatory counterparts in other countries, and they don't necessarily obviate the need for us to do inspections. We will often subsequently go and do that. But they provide us a great deal of assurance when we are using regulatory discretion to allow temporary importation of a critical-need product.

We don't do that lightly. We look very carefully at what we should know from other countries' inspections about that particular product, and we haven't used it—it's not the first thing we try to do when we're addressing a shortage, but it is an extremely important tool.

Senator BENNET. Actually, while we're on that topic, just out of curiosity, what do we know about drug shortages in other countries?

Dr. KWEDER. This is not a uniquely U.S. problem. This is occurring in other countries as well, and they utilize many of the same tools that we do to try and resolve them. We have monthly teleconferences with some of our regulatory counterparts, particularly the EU, Australia and Canada, to share information about shortages, and we work together to try and identify alternate suppliers, other creative solutions.

Senator BENNET. Are there differences in the categories of drugs that are in short supply in other places?

Dr. KWEDER. I would say, in general, it varies a lot. Sometimes there is a lot of overlap. Sometimes there's not much overlap at all. Categories, I would say they're similar. Drugs that are hard to produce or that require specialized facilities to produce are much more vulnerable to this.

Senator BENNET. Dr. Glied, do you have anything you'd like to add to that?

Ms. GLIED. Different countries have responded that they have shortages in different areas. We essentially share a supply chain with Canada, so they tend to have shortages in exactly the same areas that we do. When you go to countries like Australia that are farther away, their markets are operating somewhat differently. But I would agree with Dr. Kweder, that some of these drugs, ones where it's really hard to ramp up production because the facilities are specialized, are always going to be the ones most prone to shortages in every country.

Senator BENNET. Thank you very much, both of you, for your work on all of this. And, Mr. Chairman, thank you for holding this hearing.

Senator ENZI. Senator Whitehouse and then Senator Blumenthal.

Senator WHITEHOUSE. Thank you, Chairman.

We've spoken quite a lot about the gray market in the course of this hearing. Could either of you describe for me what the gray market looks like, or is there a report that is not in the record of these proceedings that has taken a look at what the gray market looks like and who is participating and what their motivations are?

Ms. GLIED. We have not done a report on the gray market. I believe there is a report. I think the group purchasing organizations have put out a report on the gray market. I'm not absolutely sure.

The gray market is a market that is buying drugs, often not directly from the manufacturers, often from suppliers, from providers who have extra capacity, we've been told. Some of these might be infusion clinics or somewhat—they're not necessarily the hospitals and physicians who are participating in the typical GPO arrangements. It's a very fragmented market. There are a lot of players in it, but I think we don't know very much about it because it's gray.

Senator WHITEHOUSE. For the record, doctor, I see your head nodding in agreement?

Dr. KWEDER. Yes, my head is nodding in agreement. We don't know a lot about it I think because, as Dr. Glied said, from the reports that we get, it does seem to be quite fragmented. For example, one of the ways that health care providers will learn about a product is they'll receive a fax in their office from some source advertising availability of a drug that's in shortage at an exorbitant price. In fact, I can tell you I did my fellowship training at Women and Infants Hospital, and some of my colleagues there have sent me some of these things that we have passed on.

Senator WHITEHOUSE. The gray market could include something as benign as Women and Infants Hospital calling around to other hospitals and saying we're short on this drug, do you have any to spare and would you sell it to us, which I think everybody in this room would think is a pretty benign form of trying to resolve the drug shortage issue. But it could also involve speculators who are—I see two heads nodding actively, just for the record—who are actively engaged in buying these products for the sake of hoarding them, selling them, and profiteering off of the shortage.

Dr. KWEDER. Yes. It's the profiteering that really raises red flags. It's not unusual in a community for one hospital to be in short supply of a particular product—maybe they've just used more this month than last—and to seek availability from another local facility. That isn't what we worry about. We worry about the latter.

Senator WHITEHOUSE. And I suppose you could make a case that given these shortages, and given the fact that hospitals and providers can misjudge how much they're going to need, there's actually a healthy role for a broker to be in the middle of this and find a profitable niche as a market maker.

On the other hand, if they're sending unsolicited faxes and they're seeking to charge a significant markup, it begins to look pretty sordid. What type of practices are you seeing out there at the worst end of the spectrum?

Even anecdotally.

Ms. GLIED. Just one of the things that I would also note is that one of the concerns in the gray market is that the quality of the goods, their pedigree, knowing what they actually are, is much harder to ascertain. So when these are purchased through traditional distribution channels, everybody has a good sense of what they're getting. And I think another concern with the gray market is also just the quality concerns. I just want to note that. We haven't heard reports of specific issues with the gray market. You might have heard more.

Senator WHITEHOUSE. And in terms of price gouging, what anecdotally are you hearing as the worst case scenarios that are taking place?

Dr. KWEDER. We have heard of 100-fold price increases.

Senator WHITEHOUSE. Not 100 percent, 100-fold.

Dr. KWEDER. One-hundred-fold price increases.

Senator WHITEHOUSE. A $4 drug going for——

Dr. KWEDER. A $4 drug going for——

Senator WHITEHOUSE [continuing]. Four hundred dollars.

Dr. KWEDER [continuing]. Going for $400, or $4,000. I mean, those are the kinds of reports that we hear of, and I think those are the ones that stand out, and probably many of them aren't quite to that extent. But those are the kinds of reports that many of your colleagues' constituents have sent in letters to us.

Senator WHITEHOUSE. I'll close because my time is expiring. But it strikes me that the two considerations are related in that an entity that is willing to engage in that kind of gouging is probably not morally opposed to selling low-quality or phony product as well for that kind of a markup.

I'll yield back. Thank you, Mr. Chairman.

Senator ENZI. Thank you.

Senator Blumenthal.

Senator BLUMENTHAL. Thank you, Mr. Chairman. And thank you both for your work and for your testimony today. I want to just take forward some of Senator Whitehouse's questions.

In fact, there has been a report very recently by Premier which showed that in a 2-week period, 2 weeks, beginning of this year, 1,745 examples of gray market offers from 42 acute care hospitals, an average mark-up of 650 percent, and we're talking here about drugs that are absolutely critical in oncology, in cardiology, in emergency rooms. These workhorse medicines are not luxuries. They are essential critical care medicine, and someone is profiting. It is more than a symptom. It is more than just a by-product. It is part and parcel of a market that isn't working.

Dr. Glied, you have said that there is a degree of concentration here that isn't seen in many other markets. That is a very polite way of saying that there is no competition. We have had a discussion here for close to 2 hours, an hour-and-a-half, and the word "competition" so far, at least so far as I've heard, has not been mentioned. There is no competition here, which leads to these gray markets.

So my initial question to you is, how many findings in the 2 months since the President's order have been referred to the Department of Justice by the FDA?

Dr. KWEDER. I will have to get back to you on that, on the specific number.

Senator BLUMENTHAL. Do you know of any?

Dr. KWEDER. Yes, I do.

Senator BLUMENTHAL. How many do you know of?

Dr. KWEDER. I know of at least two, but I think there are more, and I'll have to get back to you on that.

Senator BLUMENTHAL. I think that is very, very important, and as much detail as you could provide I would appreciate.

Don't you believe that some kind of overarching and intensive investigation is necessary here by either the FTC or the Department of Justice?

Dr. KWEDER. Let me just add that price gouging isn't something that would necessarily be reported to FDA. The information, the reports—the kinds of things that our Drug Shortage Program hears about is mostly hearing from companies, sometimes from health care providers or hospitalists.

The specific report on the price they paid, that isn't something they'd bring to our attention.

Senator BLUMENTHAL. I understand that you may not receive all of the reports, but the President's order directs that you consult and—

Dr. KWEDER. When we do, we do—

Senator BLUMENTHAL. You do give that information to the Department of Justice.

Dr. KWEDER. Yes.

Senator BLUMENTHAL. That's why I'm asking you. Don't you think that there is a need for an investigation here by the FTC or the Department of Justice in light of these absolutely astonishing and appalling markups as part of the gray market?

Dr. KWEDER. It's not for me to decide who should do it, but I do think that we would like to understand this better.

Senator BLUMENTHAL. Well, I would take that as a yes, unless you disagree. And I recognize——

Dr. KWEDER. You can take that as a yes.

Senator BLUMENTHAL. Thank you. Do you know who is profiting?

Dr. KWEDER. We do not know because we don't understand the whole lay of the land. There are certainly—there is a system out there of legitimate wholesalers and distributors. Whether those are the same parties who are in the business anyway who are involved in this, or whether there are just sort of people coming in and out of the landscape, we just don't know.

Senator BLUMENTHAL. So it could be the manufacturers?

Dr. KWEDER. I guess it could be, but we don't have any reason to think that it is.

Senator BLUMENTHAL. And it could be the wholesalers or distributors?

Dr. KWEDER. That's right. We just—

Senator BLUMENTHAL. And it could be the hospitals.

Dr. KWEDER. We just don't know.

Senator BLUMENTHAL. So there really is a need for some kind of fact-finding here on a broader basis than just an individual finding of a particular drug being in shortage.

Dr. KWEDER. Yes, and we understand—I mean, one of the reasons it's called—it's not black or white, it's gray. It's also gray, as Dr. Glied said, because we don't understand it very well. And so having a really clear picture of how this operates, who is involved, and what the factors are that are motivating it and rewarding it would be very helpful.

Senator BLUMENTHAL. I am almost out of time, but I just want to suggest, and you should feel free to disagree, that at the very minimum there ought to be a ban on any secondary sales—that is, sales after the initial purchase—at a price higher than that initial purchase of these kinds of drugs, which would be a remedy against this kind of hoarding and profiteering and gray market. In other words, a hospital or a wholesaler or anyone that purchases the drug should not be permitted to sell it at a higher price than it was originally purchased. That's the basic concept. I recognize there will be a lot of elaboration on it, but I'd just open it for your comment, if you have any.

Ms. GLIED. I think it's something that we should definitely take under consideration and talk to the folks at the DOJ and FTC about how that might work.

Senator BLUMENTHAL. Thank you, Mr. Chairman.
The CHAIRMAN [resuming the chair]. Senator Casey is next.
Senator Casey.

STATEMENT OF SENATOR CASEY

Senator CASEY. Mr. Chairman, thank you very much. I appreciate you having this hearing, and I appreciate the work you've done, and the Ranking Member, and so many others on both sides of the aisle at a time when we have a lot of news stories, many of them based upon the reality of Washington about how Democrats and Republicans don't work together. This is one issue where you've had I think a broad consensus, and not just for purposes of a hearing but over many, many months now to come together, and I've been so honored to work with people in both parties, working on the original legislation that Senator Klobuchar and I introduced, and I know I missed her presentation today, so I'm first of all apologizing for that. I've been in and out of the hearing.

I want to thank our witnesses. The gravity of this is hard, really hard to fully comprehend or fully articulate because this is so immediate and so grave for families. I would like to recite a story, and I'll abbreviate this, but it's the story of Sarah Batalka. She's a 29-year-old woman from Pennsylvania, and here's what she wrote to me, and I'm reading in part.

She said,

> "In April of this year, I got the worst possible news. There's a drug shortage crisis nationwide. I was told by my home infusion company that their supply of magnesium sulfate, a key ingredient in my IV bags, and one without which I cannot survive, was dwindling, and that they had only enough to fill the IV bags for a few more weeks."

She goes on to say,

"To give you some idea of the impact of this news on me, please consider what it would feel like to you if someone told you that there would be only enough air supply left for 3 weeks of breathing."

That gives you a sense of the intensity and proximity of the threat that people feel.

I also will note, and I'll introduce Dr. Maris later for the next panel, but a lot of his testimony, working as he does so well at Children's Hospital in Philadelphia, is about the impact on children, children with leukemia, and all of the horrors and nightmares those children live through and their families.

This is about as urgent as it gets for work that we're supposed to be doing in Washington.

Let me just try, in the remaining time I have, to just get to a couple of questions.

Dr. Glied, and I know you're speaking from the vantage point of Health and Human Services, I want to ask you, in your testimony you said that many—and I'm paraphrasing here—but many of the current supply problems will be alleviated when new capacity comes online. I know you may have addressed this more than once, but I want to make sure that I understand.

How do you arrive at that assessment? I didn't read your exact words, but how do you arrive at that assessment that you think this will be alleviated when new capacity comes online?

Ms. GLIED. When we spoke to the generic manufacturers, and also just read news reports and looked at information from the FDA, we learned that several of the manufacturers are planning to build or are already building new manufacturing capacity and upgrading their existing capacity. Our analysis suggested that the big problem here is that the existing capacity is just not enough to really be able to manage, to produce the amount of drugs that there's now a demand for with a sort of sufficient cushion to be able to deal with quality problems that may come up or changes in other manufacturers' production lines and other things like that.

We really need to have that extra capacity come on before we can really solve this problem. We can manage it until then, but it isn't going to go away by itself until that extra capacity is there.

Senator CASEY. OK. What a lot of us are worried about, including you and everyone here, is that there may not be an alignment between that capacity coming online and the urgency of the problem when you have only weeks within which to solve a shortage problem.

Let me just ask it this way. Tell us whether it's responding to us or responding to Sarah, whom I just quoted a moment ago, or anyone else, tell us what are the things we've got to do in the next couple of weeks or months to address this problem.

Ms. GLIED. What we have to do in the short run is really help FDA try and manage the situation we're in right now, which is one of limited capacity and big demand. We can't produce more. What we have to do is align what we're producing better with the need, and that's what we have to do in the short run.

Senator CASEY. Dr. Kweder, did you have something to add to that?

Dr. KWEDER. I think what we need to do is get companies who are experiencing production problems to engage with us early and not wait until they have a critical situation. We have learned by doing this for years now that it may not address 100 percent of these circumstances, but boy, does it help us mitigate them and prevent them. Preventing shortages is absolutely what we should be looking at.

Senator CASEY. Thank you.

[The prepared statement of Senator Casey follows:]

PREPARED STATEMENT OF SENATOR CASEY

Mr. Chairman, I would like to thank you and Ranking Member Enzi for convening this hearing today. The unprecedented growth in prescription drug shortages is among the most pressing and serious issues confronting the American health system. It is unacceptable that we are unable to help seriously ill patients not because we don't know how, but because we don't have enough of a product that we know saves lives to go around. How can this be happening in our country? We cannot allow this to happen on our watch.

This is a problem that was brought to my attention in the fall of 2011 by a hospital in Pennsylvania: Lancaster General. Since that time, I have heard from more than 50 hospitals and phar-

macists in the State about how the drug shortage crisis is affecting their ability to provide care. I am glad that we have a witness here today, Dr. John Maris from the Children's Hospital of Philadelphia, to talk about how this issue has impacted children, who are among our most vulnerable.

I have also heard from individual patients themselves, about how this crisis is affecting their health and—quite literally—their lives. I would like to share a story that I received from a constituent, which describes the severity of these shortages and how urgently we must work to address these issues.

Sarah Batalka, a 29-year-old woman from Quakertown, was born with a mitochondrial disease. For 6 years now, she's needed help maintaining her blood levels of critical electrolytes, including magnesium and potassium. In addition to receiving them in pill form, she gets them through IV's that provide enormous doses of magnesium and potassium daily. These intravenous medications keep her alive. She cannot survive without them.

Now I would like to read from a letter she wrote to me, so you can hear her own words. She writes:

> "In April of this year, I got the worst possible news: there is a drug shortage crisis nationwide. I was told by my home infusion company that their supply of IV magnesium sulfate, a key ingredient in my IV bags and one without which I cannot survive, was dwindling and that they only had enough to fill my IV bags for a few more weeks. To give you some idea of the impact this news had on me, please consider what it would feel like to you if someone told you that there would only be enough air supply left for you for 3 weeks of breathing. *I so depend on this medication for survival that its unavailability would indeed be the same as you having your air supply cutoff.*
>
> My home infusion company explained to me the reasons for the shortage. They told me that the FDA had to shut down plants that manufacture IV magnesium sulfate due to quality control issues: visible particulate matter had been found in what is supposed to be a sterile, injectable drug. I was also told that this has created a nationwide shortage, affecting individuals like myself who depend on IV nutrition and/or electrolytes . . . cancer patients, expectant mothers . . . , dialysis and kidney transplant patients, and others. IV Magnesium sulfate is, especially in cases such as mine, a life-sustaining drug needed by many different kinds of patients with many different medical conditions. *There is no substitute for IV magnesium sulfate for us, just as there is no substitute for oxygen, and you can't survive without it. I was shocked to learn that it was even possible for there to be a shortage of such a drug in our country. From what I understand, this is only one example of one drug on a list of hundreds of life-sustaining medications that are currently unavailable."*

With little than 2 weeks supply left of her medication, *twice this year* Sarah has had to reach out to our office for help in finding her medication. Fortunately, in Sarah's case, her home infusion company was, at the last minute both times, able to purchase enough IV magnesium sulfate to keep her alive for the time being.

But what will happen tomorrow? That is the question that is before us today and I pray that we can find a way to ensure that we move beyond this crisis.

Chairman Harkin, I know our staffs have been working with others in the bipartisan work group deliberatively on this issue for many months now, and are working on recommendations for how the HELP Committee can help solve this crisis. I hope that we can find a way to move forward on the legislation—S. 296, the Preserving Access to Lifesavings Medicines Act—that Senator Klobuchar and I introduced earlier this year, as I believe having an early warning system in place is fundamental to addressing these issues.

I have spoken with others of you on the committee, including Senator Blumenthal, about this crisis and I know that many of you share this same commitment to moving this legislation forward, and identifying additional solutions to advance rapidly through the FDA reauthorization or otherwise.

I look forward to working with you, and learning more from our witnesses today.

The CHAIRMAN. Thank you, Senator Casey.

Senator Hatch.

STATEMENT OF SENATOR HATCH

Senator HATCH. Thank you, Mr. Chairman.

Welcome to both of you. We appreciate the work you do and appreciate you being here.

As I've been reviewing this, there are a number of reasons for these shortages that have been given. For instance, manufacturers have asserted that current shortages are principally due to manufacturing capacity being temporarily restricted, primarily due to FDA regulatory actions. Doctors, hospitals, and some patients have suggested that the problem is due to economic factors, focusing on the adequacy of payment rates for the products. And, of course, government-mandated rebates have lowered the payment levels for these products to a point where they say they're no longer cost effective for manufacturers to produce them, or at least make investments in updating manufacturing capacity to comply with current FDA supply requirements. Others say that the FDA has asserted that the problem principally lies with a recent increase in the number of generic drugs that has exceeded existing manufacturing capacity.

Now, some outside experts point to the FDA's recent actions to review unapproved drugs, that were on the market prior to the current regulatory requirements, as being contributors to the shortage problem as well. I might say some analysts and stakeholders have blamed wholesalers for contributing to the shortage problem by rapidly increasing prices when drugs are in short supply, and I'm sure there are other arguments that are made as well.

It's a complex set of problems.

Let me just ask you this, Dr. Kweder. The agency announced yesterday an interim final rule that will expand to the current definition of sole manufacturers to increase the number of manufacturers that are required to notify FDA about a discontinuation of prod-

uct. Now, does the Executive order issued by the President and the interim final rule published by the agency, does that negate congressional action to address shortages, or is more required to mitigate current and future shortages?

Dr. KWEDER. Senator, the interim final rule really only clarifies and expands what we have as existing authority. That is very, very narrow. It really speaks to notifying FDA of a disruption or discontinuance of any type of a product where a company is the sole supplier of that product. The majority of shortages and potential shortages that we are trying to cope with don't fall into that category. So it really is not the sole answer. We think this will help, but it is not the sole answer. We can't do this on our own.

Senator HATCH. OK. Let me just say it's apparent that we have to do something here. The question is what. I listened to Senator Blumenthal's suggestion. It seems to me that would take away the desire to even be in the drug delivery business, and it would certainly put even more fiscal controls.

On the other hand, we've got to do something to maybe make sure that these drugs—for instance, it's said that 80 percent of the shortage really is in the area of sterile injectables, and these are really important for people with very serious maladies. And part of the problem, they claim, is the reduction in price for these products, and I'm not sure that's a good argument. But I'd like to get your opinion on that, if either one of you can comment.

Ms. GLIED. I think our analysis suggests that it's not a problem of a reduction in price, that prices are actually rising for those drugs that are in shortage, and that prices paid to manufacturers, that's really not been a source of this problem. We look at information from the manufacturers, as well as from public sources, and those sources seem to suggest that these manufacturers see a robust market ahead of them and that price is not the issue.

Senator HATCH. Let me just ask one other question. For example, irinotecan, lost patent protection in February 2008, as I understand it. At that time, nine generic competitors were competing in the market. The Federal reimbursement in Medicare in the second quarter of 2008 was $126.24 per dose.

Today there are only three manufacturers left in the market, down from a high of 15 manufacturers. Reimbursement by Medicaid is now $4.66 per dose. How can we increase the manufacturers in the market when we've reduced the reimbursement over 90 percent? And I understand the desire to reduce the reimbursement cost, but it seems kind of ridiculous to me.

Ms. GLIED. I just want to point out that that reimbursement cost, whatever it may be, is not the price that's paid to the manufacturers. That's a reimbursement that's paid to providers and hospitals, but they get their drugs through contracts that group purchasing organizations negotiate with manufacturers, and those contracts have only one price in them, regardless of who the payer at the end is. The fact that the price is changing, the fact that the price at the hospital or provider is changing is really disconnected from the price received by the manufacturers.

I would point out that the other thing to note is that when a drug moves from branded to generic, it takes a while until the information that Medicaid and Medicare get on prices adjusts. We

know that when prices move from branded to generic, their price falls a lot, and that's because of the patent expiration. That would not be reflected contemporaneously. So the price, that high price that you're seeing is the price that still reflects when the drug was on brand, not the price that existed when the drug went off patent.

A big piece of that, a big chunk of the reductions in prices is the fact that patent expirations are happening and drugs are moving from the branded to the generic market.

Senator HATCH. What is the price on that for the manufacturer today?

Ms. GLIED. I couldn't tell you, and I'm not even sure that that would be publicly available knowledge. Those are private contracts.

Senator HATCH. All right. Maybe that's not the way we should look at it, then.

My time is up, Mr. Chairman. I didn't mean to go over.

The CHAIRMAN. That's fine. Thank you, Senator Hatch.

Senator Hagan.

STATEMENT OF SENATOR HAGAN

Senator HAGAN. Thank you, Mr. Chairman, and thank you and Ranking Member Enzi for holding this hearing today.

I'm concerned, obviously, about this issue, and I've got a particularly heart-wrenching story I wanted to share, Mr. Chairman.

A woman, Ms. Sheets, had recurrent breast cancer, and she lived in the Winston-Salem area of North Carolina. The second time her breast cancer returned, it also affected her liver. And she was on doxo, and her doctor said that when a patient is being treated for metastatic breast cancer and is improving or stable, they continue the same therapy until they progress, which for first-line therapy could be a year. And when doxo became in short supply, her doctor waited to see if it would become available rather than switching her course of treatment.

But after 1 month, this woman had to be started on another type of treatment, and for her, a less-effective drug, and sadly, her breast cancer metastasized to her brain very soon after the initiation of that regimen, and then she died within 3 weeks of that diagnosis. This is obviously a very tragic story, and we continually hear from cancer patients like this across the State. And so I'm looking forward to seeing what we can do about this issue.

Dr. Kweder, I'm very concerned about the drug shortages that are currently affecting the way we treat patients in our country, just like Ms. Sheets. And the President's recent Executive order directed the FDA to expedite its regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes whenever it determines that expedited review would help to avoid or mitigate existing or potential drug shortages.

However, I am aware that applications for generic injectable drugs currently on the drug shortage list have been pending with the agency for more than 2½ years.

What is FDA doing currently to expedite review of applications for drugs that are currently on the drug shortage list?

Dr. KWEDER. Senator, we are absolutely expediting those. What we do is when we see a potential drug shortage—we don't wait

until there's a shortage. When we have information about a circumstance in a company that might lead to a drug shortage, we look at our queue, which is long, of generic applications for all kinds of things, and we go in and we try to find any application that we might expedite that might address that particular circumstance.

Sometimes the companies come to us and they tell us, "You know, I've had this application pending. It wasn't critical before, but it appears that it is now." And we will go right in and pull it out of the queue and address it and can turn things around in a matter of weeks to months and get it done.

Senator HAGAN. I've specifically heard from a company that is on the list for 2½ years for this generic injectable.

Dr. KWEDER. And that may well be the case, but they may be one of five producers of a generic injectable and not one that we would necessarily see as a high priority to pull out.

Senator HAGAN. But the drug is on the drug shortage list.

Dr. KWEDER. The drug is on the drug shortage list? If it is on our list of potential drug shortages, problems that might lead to shortage, we would pull that. And if there is a company that's in that circumstance and we've missed it, we need to know about that.

Senator HAGAN. OK. We will definitely get back to you on that one.

Dr. Kweder, how has the FDA prioritized addressing the drug shortage problem as part of its agency's goals? And what do we need to do, what does the FDA need to do in order to make this a priority? For example, more authorities? More resources? Et cetera.

Dr. KWEDER. We have done a great deal since the Executive order came out at the end of October. We've doubled, more than doubled the size of our Drug Shortage Program that does all the coordinating related to this. I'm happy to say we have—

Senator HAGAN. You have more than doubled—

Dr. KWEDER. The size. As of October 31, we had about four-and-a-half people on it. We now have eight and are expecting three more in January coming on board, I'm happy to say. A number of commissioned officers are joining this program. The Administration also has announced its support for the bipartisan legislation, some of which we heard about from Senator Klobuchar this morning, that would give us more authority to require companies to notify us early if they have any problem with manufacturing or otherwise that could result in a drug shortage. That is where we can make a difference.

In the long run, Dr. Glied is right, better production facilities that are more reliable and can produce high-quality products consistently is what will really address the big picture. But in the interim, FDA knowing about these potential situations, companies coming to us allows us to work with them, prioritize the work in a way that allows us to intervene and prevent the shortage in the first place.

Senator HAGAN. How many manufacturers have actually come forward to notify you of coming shortages?

Dr. KWEDER. We have had, since October 31 and the Executive order and our other activities, we have had 61 notifications mostly

from companies, some from hospitals and other things, but 61. The important thing is that that's over the course of about a month to 6 weeks. Our usual rate is about 10 notifications per month. And we know that companies have been reluctant to come to us. They don't want to draw attention to themselves. But we are seeing a real move in the industry. The Generic Drug Manufacturing Organization is helping get the word out. We're trying to work together to solve these problems before they occur.

Senator HAGAN. Thank you, Mr. Chairman, and we will definitely be following up with you. Thank you.

Dr. KWEDER. Thank you.

The CHAIRMAN. Thank you, Senator Hagan.

Senator Mikulski.

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Mr. Chairman, I know the hour is late. This has been a very needed conversation and I look forward to reviewing the testimony. I suggest we move to the next panel. I ask that my opening statement be included in the record.

There is such compelling interest in this issue in Maryland from iconic institutions like Hopkins and the University of Maryland, both research and clinical practice, and to all those wonderful doctors that just want to make sure their patients have what they need when they need it.

So let's move on with the panel and move on with an action plan.

[The prepared statement of Senator Mikulski follows:]

PREPARED STATEMENT OF SENATOR MIKULSKI

Thank you Chairman Harkin and Ranking Member Enzi for having today's hearing on prescription drug shortages. This is a local, State and national problem that, unfortunately, affects all of us.

I am glad to be a member of the bipartisan Drug Shortage Working Group, where our job is to ensure that we have the right legislative framework with the right enforcement teeth in place to ensure that our Nation's patients and health care providers are able to access the prescription drugs they depend upon.

I have heard from Maryland hospitals, doctors, nurses and patients that drug shortages are a serious problem with serious consequences.

Maryland hospitals are seeing shortages of over 100 drugs. These shortages affect patient safety and patient care. There are poor patient outcomes due to delayed treatment. Doctors and nurses are forced to use drugs that they aren't familiar with, which can lead to medical errors.

Maryland hospitals—being the innovators they always are—have implemented some regional solutions to manage the problem. The University of Maryland and Johns Hopkins University are working with the Veterans Administration to open up their pharmacies to each other to manage shortages and minimize harm to patients.

Like many complex issues, our Nation's drug shortage problem has many root causes.

There is poor product quality. Manufacturers can't—or aren't—complying with Food and Drug Administration (FDA) good manu-

facturing practices. The FDA has more advanced science and testing capabilities and are catching more quality problems than in the past.

Manufacturers can't access raw materials.

Business and market forces are affecting drug availability. Manufacturers close plants when problems arise and stop producing drugs that aren't profitable. Some drug companies have expanded the number of products they manufacture without a corresponding expansion in production capacity.

Wholesalers and health care providers aren't maintaining a large inventory of drugs to carry them through a supply disruption.

The FDA lacks authority to require notification from manufacturers when a plant shuts down, which could lead to a drug shortage. Patients and hospitals are then caught off-guard and get little or no notice that a shortage is imminent. This leaves hospitals and patients with no time to prepare and leaves the FDA with no time to find a solution, such as working with another manufacturer to increase production of the drug in shortage.

Bad actors in "grey markets" are selling fake, expired or illegally imported prescriptions. Some are hording drugs and hiking up the prices—exacerbating the problem.

President Obama issued an Executive order on October 31 to immediately take action to reduce shortages; but we can and must do more.

I have heard from stakeholders about potential solutions including: penalties for price gouging; requiring manufacturers to give notice when there is a manufacturing issue that could cause a shortage, which is what Senator Klobuchar's bill would do; improve coordination and consultation among FDA review, inspection and compliance staff to get more manufacturers to enter the market and get manufacturing lines re-inspected and running again in order to reduce the likelihood of shortages.

I look forward to hearing from the witnesses about their recommendations and will fight to include the best solutions in the Prescription Drug User Fee Act.

The CHAIRMAN. OK. Thank you very much, Senator Mikulski.

I thank the panel. You've been very, very excellent witnesses. Thank you very much for your work and for being here.

Now we'll call our next panel, Dr. Marcia Crosse, Mr. Murray Aitken, and Mr. Ralph Neas.

Dr. Marcia Crosse, Director of Health Care for the Government Accountability Office. Dr. Crosse has been at GAO since 1983, has extensive experience evaluating areas such as biomedical research, medical product safety, and pharmaceutical regulations. Most recently she led the team that issued today's GAO report on drug shortages.

Murray Aitken is executive director of the IMS Institute for Health Care Informatics. In this position, Mr. Aitken collaborates with other experts in the public and private sectors to provide information services and analytics for the health care industry. He led the team at IMS that published a report in November entitled "Drug Shortages: A Close Look at Products, Suppliers, and Volume Volatility."

Next we have Mr. Ralph Neas, president and chief executive officer of the Generic Pharmaceutical Association. Mr. Neas has spent his career focusing on civil rights and health issues, having previously served as the executive director of the Leadership Conference on Civil Rights, and most recently as the CEO of the National Coalition on Health Care.

We thank all of you for being here.

I'm going to yield to Senator Casey for purposes of introducing our final witness, Dr. Maris.

Senator CASEY. Thank you, Mr. Chairman.

Dr. Maris, welcome. Welcome to the whole panel. I haven't had a chance to personally say hello to Dr. Maris today because I can't reach that far, but we'll say hello after the hearing.

Dr. Maris is chief of the Division of Oncology at Children's Hospital of Philadelphia and the director of the Center for Childhood Cancer Research. He's also the director of the Pediatric Oncology Program at the Abramson Cancer Center at the University of Pennsylvania. He's nationally and internationally recognized for his work in translating research about childhood cancers from the labs to the patients. His team at Children's Hospital has been able to identify the main genes associated with neuroblastoma, a cancer that can be extremely aggressive. In the quest for a cure, they have moved some of these discoveries toward new therapies, a number of which are now in clinical trials.

Dr. Maris, we're grateful for your work, and thank you for being here today with us.

The CHAIRMAN. Thank you very much, and thank you all for being here. Your statements will be made a part of the record in their entirety. We'll go from left to right. If you could limit your opening statements to 5 minutes, we'd certainly appreciate that.

Dr. Crosse, welcome and please proceed.

STATEMENT OF MARCIA G. CROSSE, Ph.D., DIRECTOR, HEALTH CARE, GOVERNMENT ACCOUNTABILITY OFFICE, WASHINGTON, DC

Ms. CROSSE. Thank you, Mr. Chairman. Mr. Chairman and members of the committee, I'm pleased to be here today as you examine prescription drug shortages. As you stated, Mr. Chairman, today you're releasing GAO's report on FDA's handling of drug shortages prepared in response to a request from you, Senator Casey, and Senator Blumenthal. I will discuss some of our findings from that report.

As we've heard, the number of drug shortages has grown substantially, more than tripling in the last 5 years, and drug shortages are currently at record levels. Over half of the critical shortages involve generic injectable drugs with certain therapeutic classes such as anesthetic, oncology, and anti-infective drugs among those most often in short supply. Our review of specific shortages shows that the majority were caused by manufacturing problems which are particularly likely to occur with sterile injectable drugs.

My remarks today will focus specifically on what FDA can and cannot do to respond to drug shortages, and how the agency has responded when drug shortages have occurred. We've heard from

FDA about some of the things that they can do, and I'll come back to that. But what is it that FDA cannot do?

FDA cannot require manufacturers to report actual or potential shortages to the agency or the public, or require manufacturers to take certain actions to prevent, alleviate, or resolve shortages. FDA cannot force manufacturers to make a drug or to increase the production of a drug that's in short supply. It cannot control the distribution of drugs. It cannot prevent drugs from being sold into the gray market, and it cannot control prices. These distribution concerns have frequently been highlighted in recent discussions of shortages, and hospitals are being offered gray market drugs to fill shortages at prices sometimes hundreds of times above normal.

What is it that FDA can do? Because FDA usually doesn't know about a shortage until it is well under way, the agency's approach to managing drug shortages is predominantly reactive. As FDA testified, the agency takes multiple steps to respond to drug shortages such as providing assistance to manufacturers to resolve quality problems.

In addition, FDA encourages other manufacturers to increase production. It allows some products to continue to be marketed despite labeling or quality problems, and it has occasionally permitted the import of foreign versions of drugs.

FDA may also expedite its review of relevant drug applications. The agency currently has a backlog of over 8,000 generic drug applications and told us that to try to address shortages, it expedited the review of hundreds of applications. But FDA was unable to tell us whether any of the expedited reviews were completed in time to help resolve a shortage.

Of particular importance, when FDA is informed of the possibility of a shortage in advance, the agency has increasingly been able to prevent potential drug shortages from occurring. By taking the same kinds of actions the agency uses to respond to a shortage, FDA has prevented shortages of the majority of drugs where the agency learned of potential supply disruptions in advance.

Beyond this, however, there are some things that the agency has not been doing. FDA's ability to protect public health has been limited by management challenges that weaken its ability to respond to drug shortages. Most importantly, FDA has not systematically maintained data on drug shortages. Without such data, the agency has been unable to monitor trends and enhance its ability to address the causes of drug shortages.

Many of these drugs have repeatedly been in short supply over the last decade, but FDA has not been performing routine analyses to understand patterns or examine root causes. Without a systematic method to store, track, and share data on drug shortages, the agency cannot ensure that it responds to potential and current shortages in a timely and coordinated manner.

In addition, FDA has consistently staffed its Drug Shortage Program with a small number of employees. Even while the number of drug shortages tripled, just three staff were handling this work, and FDA only recently moved to add resources to this program.

Finally, while the agency identified drug availability as a strategic objective to protect public health, this objective was focused solely on processes to bring new drugs to market. The agency had

no strategic focus on maintaining the supply of drugs already on the market.

In closing, in our report we made several recommendations to FDA to strengthen its ability to respond to drug shortages, including assessing the resources allocated to the Drug Shortage Program and developing an information system on shortages. The agency has outlined actions it plans to take that are consistent with our recommendations.

Our report also includes a matter for congressional consideration. We believe that Congress should consider establishing a requirement for manufacturers to report to FDA any changes that could affect the supply of their drugs.

Mr. Chairman, this concludes my prepared remarks. I'd be happy to answer any questions that you or other members of the committee may have.

[The prepared statement of Ms. Crosse follows:]

PREPARED STATEMENT OF MARCIA G. CROSSE, PH.D.

SUMMARY

WHY GAO DID THIS STUDY

In recent years, nationwide shortages of prescription drugs have increased, preventing patients from accessing medications essential to their care. The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), established a Drug Shortage Program with a mission of helping to prevent, alleviate, and resolve shortages. FDA receives information about shortages from manufacturers, though this reporting is generally voluntary, as well as from the American Society of Health-System Pharmacists (ASHP). ASHP tracks nationwide shortages for its members through a partnership with the University of Utah Drug Information Service (UUDIS).

GAO was asked to review trends in shortages and examine FDA's response. In this report, GAO:

(1) reviews trends in drug shortages,

(2) describes FDA's response, and

(3) evaluates FDA's ability to protect public health through its response to drug shortages. GAO analyzed UUDIS data, interviewed officials from FDA, health care professional associations, and industry, and also examined relevant statutes, regulations, information, and documents.

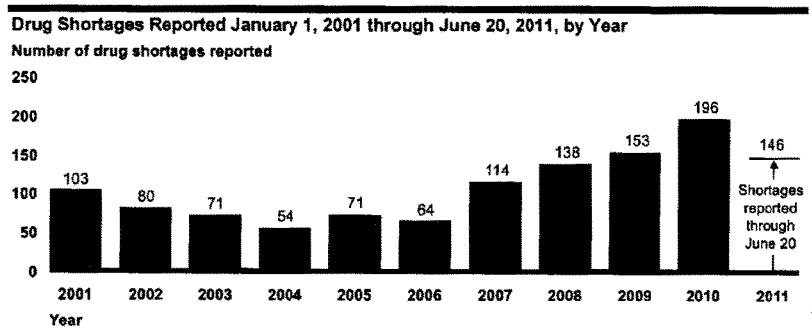
WHAT GAO RECOMMENDS

Congress should consider establishing a requirement for manufacturers to report to FDA any changes that could affect the supply of their drugs. In addition, FDA should enhance its ability to respond to drug shortages, for example, by developing an information system to manage data about shortages. HHS outlined actions it plans to take that are consistent with GAO's recommendations.

DRUG SHORTAGES—FDA'S ABILITY TO RESPOND SHOULD BE STRENGTHENED

WHAT GAO FOUND

The number of drug shortages has grown substantially since 2006. In total, 1,190 shortages were reported from January 1, 2001, through June 20, 2011, according to UUDIS data. From 2006 through 2010, the number of drug shortages increased each year. A record number of shortages were reported in 2010, and 2011 is on pace to surpass 2010's record. Of the shortages, 64 percent involved drugs that were in short supply more than once. On average, shortages lasted 286 days (over 9 months). Over half of shortages reported from January 1, 2009, through June 20, 2011, that UUDIS identified as critical—because, for example, alternative drugs were not available—involved generic injectable drugs. Certain therapeutic classes (such as anesthetic, oncology, and anti-infective drugs) were among those most often in short supply.



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

FDA responds to drug shortages by taking actions to address the underlying causes and to enhance product availability, for example by providing assistance to manufacturers to resolve manufacturing or quality problems that can result in a shortage. When informed of the possibility of a shortage in advance, FDA has increasingly been able to prevent potential drug shortages from occurring. FDA prevented 50 potential shortages during the first half of 2011. As part of its response, FDA provides general information about drug shortages to the public via its Web site.

FDA is constrained in its ability to protect public health from drug shortages due to its lack of authority to require manufacturers to report actual or potential shortages to the agency or the public, or to require manufacturers to take certain actions to prevent, alleviate, or resolve shortages. As a result, the agency's approach to managing drug shortages is predominately reactive. FDA's ability to protect public health is also constrained by management challenges that weaken its ability to respond to drug shortages. For example, FDA does not systematically maintain data on drug shortages, without which it is unable to monitor trends and enhance its ability to address the causes of drug shortages. In addition, FDA has provided limited resources to manage its response to drug shortages and lacks related performance measures and priorities.

Mr. Chairman and members of the committee, I am pleased to be here today to discuss the Food and Drug Administration's (FDA) response to prescription drug shortages. According to FDA, a record number of drugs were in short supply in 2010, and the number of drug shortages has continued to grow throughout 2011. A variety of factors can trigger drug shortages, such as disruptions in the supply of the active pharmaceutical ingredients required to manufacture the drug, manufacturing problems, manufacturers' business decisions, and increased demand for products. Drug shortages directly threaten public health by preventing patients from accessing medications that are essential to their care. During shortages, physicians may have to ration their supplies, delay treatments, or use alternative medications that may be less effective for the condition, carry unwanted side effects, or cost more. Consistent with its mission of protecting the public health, FDA, an agency within the Department of Health and Human Services (HHS), established a Drug Shortage Program to help prevent, alleviate, and resolve shortages.

Drug shortages may be reported to FDA by manufacturers, health professionals, or the public. FDA also obtains information from the American Society of Health-System Pharmacists (ASHP), which tracks and makes information publicly available about nationwide drug shortages through a partnership with the University of Utah Drug Information Service (UUDIS).[1]

My statement will highlight key findings from our November 2011 report, which is being released today, that reviews trends in prescription drug shortages and FDA's response.[2] In that report, we (1) reviewed trends in prescription drug shortages that occurred from January 2001 through June 2011, (2) identified the reported

[1] ASHP posts information about drug shortages on its Web site. See *http://www.ashp.org/menu/PracticePolicy/ResourceCenters/DrugShortages.aspx.*

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

causes of selected drug shortages that occurred from January 2009 through June 2011, (3) described FDA's response to drug shortages, and (4) evaluated the extent to which FDA is able to protect the public health through its response to drug shortages.

To identify trends in drug shortages, we analyzed UUDIS data on the number and duration of prescription drug shortages reported to ASHP from January 2001 through June 20, 2011. We examined these data because FDA did not have a database containing information on drug shortages for the time period we reviewed, and UUDIS is generally regarded as the most comprehensive and reliable source of such information. Using these data, we identified the number of drugs that had been in short supply on multiple occasions and the collective duration of these shortages. Using Red Book data, we examined the characteristics of 269 critical drug shortages that were identified during a shorter time period, January 1, 2009, through June 20, 2011.[3]

To identify the reported causes of selected drug shortages that occurred from January 2009 through June 2011, we focused our analysis on a nongeneralizable sample of 15 drug shortages that have had a significant impact on public health. The drugs involved in these shortages—all sterile injectables—are from three therapeutic classes: anesthesia, oncology, and anti-infective drugs.[4] We asked FDA officials to provide information on the causes of these 15 drug shortages, as reported to the agency by manufacturers. For additional information on the causes of shortages, we obtained information from four manufacturers of sterile injectable drugs—APP Pharmaceuticals, Bedford Laboratories, Hospira, and Teva Pharmaceuticals. All of these manufacturers produce drugs that recently were in short supply, and all of the 15 drug shortages we selected for review involved drugs that were manufactured by one or more of these manufacturers.

To describe FDA's response to drug shortages, we interviewed FDA officials and reviewed agency documents, including policies and procedures. To describe how FDA responded to the 15 selected drug shortages we reviewed in detail, we examined information the agency provided about its response to these shortages. We also analyzed FDA information on potential drug shortages the agency prevented from January 2010 through June 2011.

To evaluate the extent to which FDA is able to protect public health through its response to drug shortages, we analyzed FDA's authority under the Federal Food, Drug, and Cosmetic Act, and reviewed relevant FDA regulations, policies, procedures, and documents. In addition, we evaluated FDA's approach to managing its response to drug shortages using standards for internal control—including those for information and communications, monitoring, and risk assessment.[5] We also interviewed a variety of stakeholders—including drug manufacturers, health professional associations, and others involved in drug production and the drug supply chain—to obtain information about FDA's response to drug shortages. Our work was performed in accordance with generally accepted government auditing standards.

In brief, we found that the number of drug shortages has grown substantially in recent years, and FDA is constrained in its ability to protect the public health from the impact of these shortages.

The number of drug shortages has grown substantially since 2006, and many shortages involved generic injectable drugs. In total, 1,190 shortages were reported from January 1, 2001, through June 20, 2011, according to UUDIS data. From 2006 through 2010, the number of drug shortages increased each year and grew by more than 200 percent over this period. A record number of shortages (196) were reported in 2010, and 2011 is on pace to surpass 2010's record, with 146 shortages reported through June 20, 2011. Over half (64 percent) of the 1,190 shortages represent 283 drugs that were in short supply more than once. On average, these 283 drugs were each in short supply between 2 and 8 times during this period, with an average of 2.7 times per drug. While the duration of all reported shortages varied considerably, most shortages lasted 1 year or less. On average, shortages lasted 286 days (over

[3] Red Book is a compendium published by Thomson Reuters that includes information about the characteristics of drug products. UUDIS recognized these shortages as critical because alternative medications were unavailable, the shortages affected multiple manufacturers, or the shortages were widely reported; because the shortages were determined to be critical, they were posted to ASHP's Web site.

[4] Specifically, we reviewed information about shortages for five anesthesia drugs (epinephrine, neostigmine, propofol, thiopental, and succinylcholine), five oncology drugs (cisplatin, cytarabine, doxorubicin, etoposide, and vincristine) and five anti-infective drugs (acyclovir, amikacin, cefotetan, clindamycin, and sulfamethoxazole-trimethoprim). Most of these drugs have been available in generic form for over 15 years.

[5] See GAO, *Standards for Internal Control in the Federal Government,* GAO/AIMD–00–21.3.1 (Washington, DC: November 1999).

9 months). Over half of shortages reported from January 1, 2009, through June 20, 2011, that UUDIS identified as critical—because, for example, alternative drugs were not available—involved generic injectable drugs. Certain therapeutic classes (such as anesthetic, oncology, and anti-infective drugs) were among those most often in short supply.

The drug shortages we reviewed in detail were generally caused by manufacturing problems and exacerbated by multiple difficulties. Of the drug shortages we reviewed in detail, 12 of the 15 were primarily caused by manufacturing problems, including those that resulted in manufacturing shutdowns, according to information provided by FDA and by manufacturers. For example, one manufacturer shut down a facility that produces sterile injectable drugs in order to improve the facility's manufacturing capabilities. While the manufacturer expected that the upgrade would take 3 months, it instead took 1 year to complete, and as a result, multiple drugs that were produced at this facility went into short supply. The remaining 3 shortages we reviewed were reportedly caused by disruptions in the supply of active pharmaceutical ingredients. Officials from FDA and manufacturers explained that sterile injectable drugs are complex to make, and as such, can be prone to manufacturing and quality problems. In addition, certain types of sterile injectable drugs, such as anti-infective and oncology drugs, can be particularly challenging to manufacture. FDA also pointed out that sterile injectable drugs are being made by a decreasing number of aging facilities, which may contribute to the recent increase in manufacturing problems. In addition to the initial problems that caused the shortages, over half of the shortages we reviewed (8 of 15) were subsequently exacerbated by multiple other difficulties that arose after the shortages began. These eight shortages were each affected by an average of four distinct difficulties that occurred in addition to the primary cause of the shortage and generally affected multiple manufacturers. During these shortages, multiple manufacturers sometimes experienced the same exacerbating issues once a shortage was already ongoing. For example, 9 of the 15 shortages we reviewed were extended as a result of manufacturing problems that occurred in addition to the shortages' primary causes. It is also important to recognize that some drugs may only be produced by a few manufacturers. The drugs involved in the 15 shortages we reviewed were produced by an average of three manufacturers at the time the drug went into short supply. According to officials from FDA and industry officials, when only a few manufacturers make a drug and one cannot maintain production, it can be difficult for the other manufacturers to substantially increase production to ensure that demand for a drug is met—even in the absence of any other problems. Officials from one manufacturer described recent shortage situations as a perfect storm of several manufacturers coincidentally experiencing manufacturing problems all at the same time.

• *FDA responds to known drug shortages by taking actions to address their underlying causes and to enhance product availability.* FDA officials explained that they respond to all of the shortages of which the agency becomes aware, and they determine how to address each shortage based on its cause and the public health risk associated with the shortage. For example, the agency may provide assistance to manufacturers to resolve manufacturing or quality problems that can result in a shortage. Our review of FDA's response to 15 shortages of sterile injectable drugs showed that FDA typically used 2 or more types of actions to respond to each shortage, and for 8 shortages, the agency responded with 4 or more types of actions. FDA most frequently offered assistance to manufacturers to prevent, alleviate, or resolve the shortage, or notified other manufacturers to expect increased demand or encouraged them to increase production. FDA has demonstrated that it can prevent the majority of shortages from occurring when it learns of potential supply disruptions in advance. FDA prevented 50 potential shortages during the first half of 2011—about 1.5 times the number of potential drug shortages (35) prevented during all of 2010. To prevent these potential shortages, FDA took some of the same types of actions it uses to alleviate and resolve shortages. As part of its response to drug shortages, FDA communicates information about shortages to the public via its Web site, which lists both current and resolved shortages.[6]

• *FDA is constrained in its ability to protect public health from drug shortages.* Specifically, FDA is constrained by its lack of authority to require manufacturers to provide the agency and the public with information about shortages, or require that manufacturers take certain actions to prevent, alleviate, or resolve shortages. FDA's sole authority related to manufacturers' reporting of drug shortages pertains to the discontinuation of approved drugs that are life-supporting, life-sustaining, or for use in the prevention of a debilitating disease or condition, when such drugs are

[6] See *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm*.

produced by only one manufacturer.[7] In such instances, companies are required to provide FDA with at least 6 months notice of discontinuations. However, such discontinuations have not been the primary cause of most recent drug shortages. As a result of these constraints, the agency's approach to managing drug shortages is predominately reactive. While FDA has encouraged manufacturers to report supply disruptions to the agency, according to agency officials, less than half of all shortages are reported to the agency by manufacturers. Instead, FDA is most often notified by ASHP, health care providers, or consumers when they are unable to purchase a drug—a point at which the shortage is already affecting public health. FDA's ability to protect public health is also constrained by management challenges that weaken its ability to respond to drug shortages. Specifically, FDA does not maintain data on drug shortages, such as their causes and the agency's response. Without such data, FDA is unable to systematically monitor trends and enhance its ability to address the causes of drug shortages. In addition, despite the increase in the number of drug shortages reported in recent years, FDA has not identified drug shortages as an area of strategic importance for the agency. It has consistently staffed its Drug Shortage Program with a small number of employees. While FDA has recognized the significant public health consequences that can result from drug shortages, the agency has not developed a set of results-oriented performance metrics related to drug shortages, and has not identified drug shortages as an area of strategic importance for the agency. Without such management tools, FDA may be unable to effectively evaluate its work and improve its ability to protect the public health.

In conclusion, the number of drug shortages has substantially increased in recent years—including those for life-saving medications such as oncology drugs—a situation that has jeopardized the public health. While FDA may not always be able to prevent shortages from occurring, the agency's response to drug shortages is constrained by its lack of authority to require manufacturers to report potential or current shortages to the agency. FDA has demonstrated that when it learns of shortages in advance, it can prevent the majority of such shortages from occurring.

However, it does not currently have the authority to require manufacturers to provide it with information about potential or current shortages, and therefore it can only prevent the shortages that it becomes aware of through voluntary reporting. FDA's ability to protect the public health is also constrained by its own management challenges. The agency has not elevated the priority it places on its response to drug shortages, despite the rapid escalation of these shortages. Not only have its resources not kept pace with this escalation, the agency has not developed the metrics to manage this growing public health problem. Without data and results-oriented performance measures, FDA cannot systematically monitor drug shortages and their causes, nor can it adequately track or assess its own success in preventing or mitigating shortages. Although FDA recognizes the serious threat these shortages pose, we believe the agency can and must do more to protect the public health.

Our report includes a matter for congressional consideration that would establish a requirement for manufacturers to report to FDA any changes that could affect the supply of their drugs. In addition, our report recommends that FDA take steps to strengthen its ability to respond to drug shortages by: (1) assessing the resources allocated to the Drug Shortage Program; (2) developing an information system to enable the Drug Shortage Program to manage its daily workload in a systematic manner, track data about drug shortages—including their causes and FDA's response—and share information across FDA offices regarding drugs that are in short supply; (3) ensuring that FDA's strategic plan articulates goals and priorities for maintaining the availability of all medically necessary drugs; and (4) developing results-oriented performance metrics to assess and quantify the implementation of the agency's goals and FDA's response to drug shortages.

In commenting on a draft of the report upon which this testimony is based, HHS stated that it supports legislation that would require manufacturers to report potential or actual supply disruptions to FDA. In addition, HHS outlined actions it plans to take that are consistent with our recommendations.

Mr. Chairman, this concludes my statement. I would be pleased to respond to any questions you or other members of the committee may have.

The CHAIRMAN. Thank you, Dr. Crosse.

Mr. Aitken, please proceed.

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[7] See 21 U.S.C. § 356c; 21 CFR § 314.81(b)(3)(iii) (2011). FDA does not have the authority to enforce this requirement, for example, by seeking civil monetary penalties. To the maximum extent possible, FDA is to distribute information on the discontinuance of these products to appropriate physician and patient organizations.

STATEMENT OF MURRAY AITKEN, SENIOR VICE PRESIDENT, HEALTHCARE INSIGHT, IMS, PARSIPPANY, NJ

Mr. AITKEN. Mr. Chairman, members of the committee, thank you for this opportunity to appear before you today on this important topic. Disruptions in clinical care caused by drug shortages are of growing concern among patients, clinicians, suppliers and manufacturers, as well as policymakers. We applaud the efforts to date of the FDA, ASPE, and ASHP, and this committee in working to understand the problem.

We believe it's critical to bring the best available information to the discussion of the underlying causes and potential mechanisms to prevent shortages or alleviate their effects. That's why the IMS Institute for Healthcare Informatics has undertaken an independent study without industry or government sponsorship, using our proprietary data to look at the actual supply of those drugs on the shortage lists maintained by the FDA and the American Society of Health System Pharmacists.

Among the findings from our analysis and included in our report are three important points. First, the drug shortage problem is highly concentrated in a relatively small number of products that are mostly generic and mostly injectables. We see that of the 168 products in our dataset, 83 percent are generics, 82 percent are injectables, and they are almost entirely used in hospital or clinic settings for inpatient or outpatient care.

While the problem may be concentrated in terms of the type of products, this is not to say the problem, of course, is small. In fact, the 168 products cover every one of the major anatomical therapy classes used to categorize therapeutic pharmaceuticals, from analgesics to injectable vitamins. And in the case of 20 injectable oncology products that are on the shortages list, these are drugs that over the course of a 12-month period were used to treat 550,000 cancer patients. So any disruption in the supply of those drugs will potentially affect a large number of patients.

We think, though, that the concentration of the problem is an important point when considering solutions. To the extent that solutions can be focused on the segment of pharmaceuticals and the part of the supply chain where disruptions are occurring, we would expect a more successful outcome and fewer unintended consequences for the rest of the health care system.

The second finding from our report is that the term "shortage" can have different meanings. For over half of the products on the shortages list, our measure of the total monthly volume being shipped to end user settings, whether it be a hospital, a clinic, a retail pharmacy warehouse, or a mail order facility, that volume has, in fact, been steady or even increasing over the past 5 years, and this suggests that at a national level there may not be an imbalance between total demand and total supply. Instead, the shortage is being experienced by a particular pharmacy or in a particular region of the country or with a particular wholesaler or intermediary. Alternatively, the shortage can be for one specific manufacturer of a product even if there is adequate supply from other manufacturers.

For the other 45 percent of the products, though, we do see at a national level evidence of significant reductions, on average 26

percent, in the monthly volume being supplied to hospitals and clinics, and even more volatility in monthly volume being supplied by individual companies. This can only mean severe disruption across the supply chain even if it is for a relatively small number of products.

The third finding relates to the suppliers of these products. We see that over half of the products have only one or two suppliers, and this means that in the event that one company has a temporary disruption of manufacturing capacity, for whatever reasons, it may be very difficult for another company to replace that volume quickly and, hence, leading to a shortage.

Our perspective on recommendations is grounded on what we know about the information and analytical approaches that can be applied to this situation. We believe a multistakeholder early warning system can be a critical tool to help the FDA, pharmacists, manufacturers and intermediaries predict, monitor, and mitigate the impact of supply disruptions. Such a system should include a systematic approach to risk identification, a continuous forecast for long-term demand for the high-risk sectors of the market, a volatility index focused on weekly or monthly changes in the supply volume, and that can be a sentinel of instability in the supply chain, and predictive modeling that helps keep a tight focus on interventions only on those specific parts of the market and supply chain that need attention.

We are grateful for the opportunity to present our perspective and we look forward to today's discussion on solutions that are balanced, coordinated, and sustainable. Thank you.

[The prepared statement of Mr. Aitken follows:]

PREPARED STATEMENT OF MURRAY AITKEN

Chairman Harkin, Senator Enzi, and members of the committee, thank you for the opportunity to contribute to the discussion of this important topic. Drug shortages have become of increasing concern for patients, clinicians, manufacturers and policymakers. While the issue is not entirely new, the increased number of drugs reported as being in short supply has precipitated a deeper understanding of the underlying causes of the problem, and potential remedies to prevent future shortages or alleviate their impact on patient care.

I am the Executive Director of the IMS Institute for Healthcare Informatics, which is focused on bringing objective, relevant insights and research that will accelerate the understanding and innovation critical to sound decisionmaking and improved patient care. We have recently undertaken a study based on analysis of IMS Health data and publicly available drug shortage lists in order to bring new evidence on the products and suppliers involved, and the volume volatility occurring in the marketplace. This work has been undertaken as a public service, without industry or government sponsorship.

METHODOLOGY OF IMS ANALYSIS

The basis of our analysis is a dataset developed by the IMS Institute and based on products listed on the Current Drug Shortages Sections of Web sites maintained by the U.S. Food and Drug Administration and the American Society of Health-System Pharmacists. Information related to products and molecules was accessed on October 7, 2011, resulting in an initial list of 197 unique products. Of these products, 11 are considered to be widely available, and a further 18 are products unable to be uniquely identified in the IMS databases, leaving 168 products in the final dataset.

For the 168 products, we accessed monthly volume and sales data for the 5-year period beginning September 2006 and ending August 2011 from IMS National Sales Perspectives. This measures volume in Standard Units and sales within the U.S. pharmaceutical market by pharmacies, clinics, hospitals and other healthcare providers. Sales amounts are based on pricing information derived from wholesaler in-

voices to end-users and does not include rebates and discounts commonly negotiated between end-users and manufacturers, including Medicaid rebates and 340B discounts.

Additional information related to distribution channel, therapy class using the Anatomical Therapeutic Chemical (ATC) Classification System, and characterization of the product as a brand, generic or branded generic was also included and derived from IMS National Sales Perspectives.

For oncology products, patient counts by tumor site and regimen were sourced from IntrinsiQ, a unit of AmerisourceBergen Specialty Group, via IMS Oncology Analyzer, for the period of June 2006–June 2011.

Regional volume usage was derived from IMS Drug Distribution Data (DDD) for the period of September 2007 to August 2011.

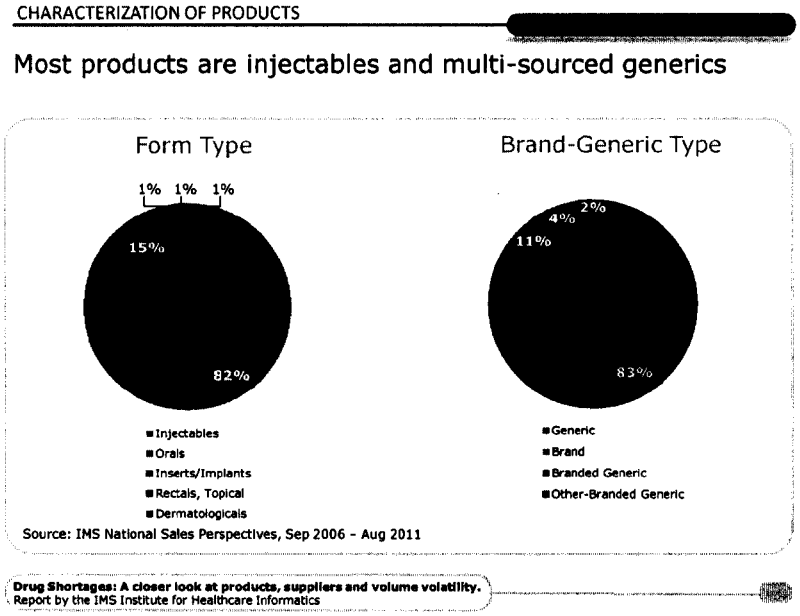
KEY FINDINGS

The key findings of our analysis relate to the characterization of the products on the shortages list; the suppliers of these products; and the volatility in supply volume for individual products.

Characterization of the Products on the Shortages List

Most of the 168 products included in the IMS dataset are injectables (82 percent) and generics (83 percent) (Exhibit 1). This points to the concentration of products to a segment of the market and suggests the underlying causes and solutions to drug shortages should be focused on this part of the overall pharmaceutical sector.

Exhibit 1



We also found that most of the products on the shortages list are used in hospital or clinic settings. For the injectables, 72 percent of the standard unit volume is supplied to non-federal hospitals, 16 percent to clinics, 3 percent to Federal facilities, and the remaining 9 percent goes to retail or other channels. For the oral products, the distribution is more directed toward retail channels, accounting for 79 percent of the volume, and only 5 percent going to hospitals and 4 percent to clinics.

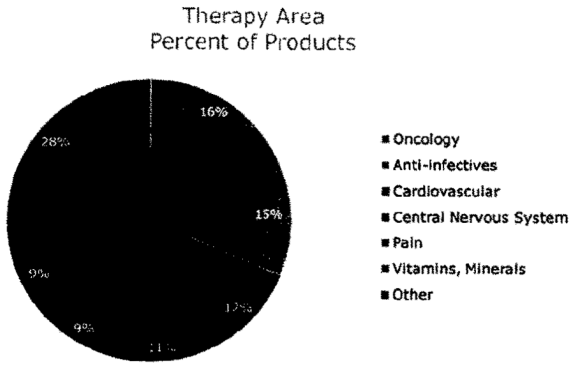
Although drug shortages are concentrated in terms of the nature of the products, they are extensive in terms of the therapy areas they are used in. In fact, the 168 products cover all of the major anatomical therapy classes used to categorize therapeutic pharmaceuticals. The largest share of products are used in oncology, representing 16 percent of the products; a further 15 percent are anti-infective prod-

ucts; 12 percent are used to treat cardiovascular disease; 11 percent for central nervous system conditions; 9 percent for pain; a further 9 percent are vitamins and minerals (mostly in injectable form); and the remaining 28 percent cover a broad range of other therapy areas including asthma/chronic obstructive pulmonary disease and immunosuppressants (Exhibit 2).

Exhibit 2

CHARACTERIZATION OF PRODUCTS [redacted]

All of the major therapy areas have products on the list



Source: IMS National Sales Perspectives, Sep 2006 - Aug 2011

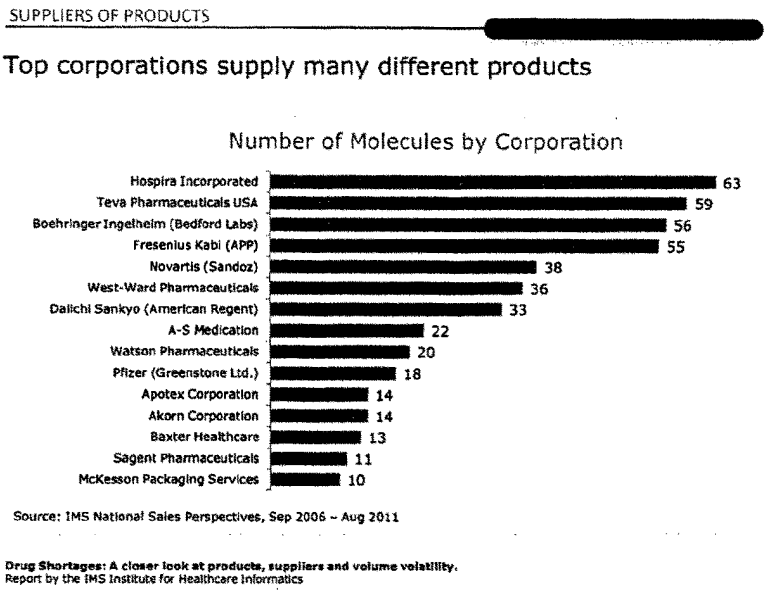
Drug Shortages: A closer look at products, suppliers and volume volatility.
Report by the IMS Institute for Healthcare Informatics

The number of patients potentially affected by drug shortages is also extensive. In the case of the 20 injectable oncology drugs on the shortages list, we estimate that 550,000 cancer patients were treated with at least one of those drugs during the past year. This therefore can represent the number of patients whose treatment could be affected by any disruption in the supply of these drugs.

Characterization of Suppliers

We analyzed the firms supplying the 168 products on our shortages list over the past 5 years. In total, 100 companies supplied one or more of the products on the current shortages list over the past 5 years. More recently, 98 separate companies controlled by 88 corporations were supplying these products during the 3 months ending August 2011. The largest generic manufacturers have multiple products (Exhibit 3).

Exhibit 3



Over time, we see a number of companies, generally supplying relatively few products, entering and leaving the marketplace. Over the past 5 years the number of corporations supplying the 168 products has fluctuated, including 13 corporations that have stopped supplying any products on the shortages list during the past 2 years. This movement among suppliers is one of the underlying causes of the disruption felt by pharmacists when they are no longer able to source their supplies from established manufacturers.

Among the 168 products on the shortages list, we identified 86 products, or 51 percent of the total, that currently have two or fewer suppliers. Of those 86 products, 56 had only one supplier, and 7 had no suppliers during the 3 months ending August 2011 (Exhibit 4).

Exhibit 4

While patent protected products have single suppliers and generally do not face supply shortages, in the generics market the relatively high number of products with very few suppliers may be a contributing factor to supply disruption. In the event that one company has a temporary disruption of manufacturing capacity, it may be difficult for another company to replace that volume quickly and hence lead to a shortage.

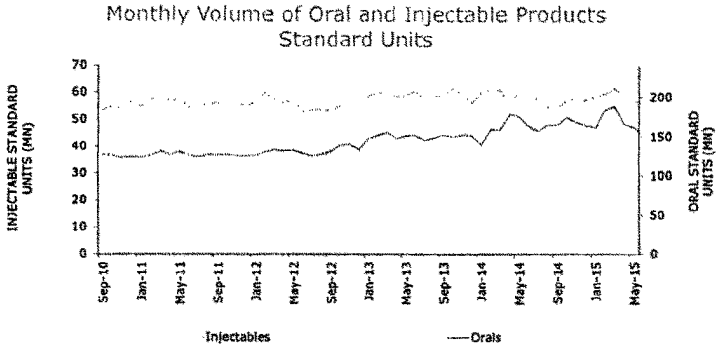
Volatility in Supply Volume

The average monthly supply from wholesalers to end-user settings for the total set of 168 products has, in aggregate, increased slightly over the past 5 years. For the injectable products, the average number of standard units supplied monthly increased from 54 million in 2006 to 56 million in 2011. For the smaller number of oral products, volume increased from 125 million to 157 million during the same reference period (Exhibit 5).

Exhibit 5

VOLUME AND SALES OF PRODUCTS [redacted]

In aggregate, injectable volume has grown 4% over the past five years



Source: IMS National Sales Perspectives, Sep 2006 – Aug 2011

Drug Shortages: A closer look at products, suppliers and volume volatility.
Report by the IMS Institute for Healthcare Informatics

A closer examination reveals that three distinct segments exist among the drugs on the current shortages list:

(a) a "declining" set of 75 products that have recent monthly supply volume of less than 80 percent of a base period defined as September 2006–August 2009;

(b) a "stable" set of 56 products whose recent monthly supply is between 80 percent and 120 percent of the base period; and

(c) a "growing" set of 31 products where monthly supply is at least 20 percent more than the base period.

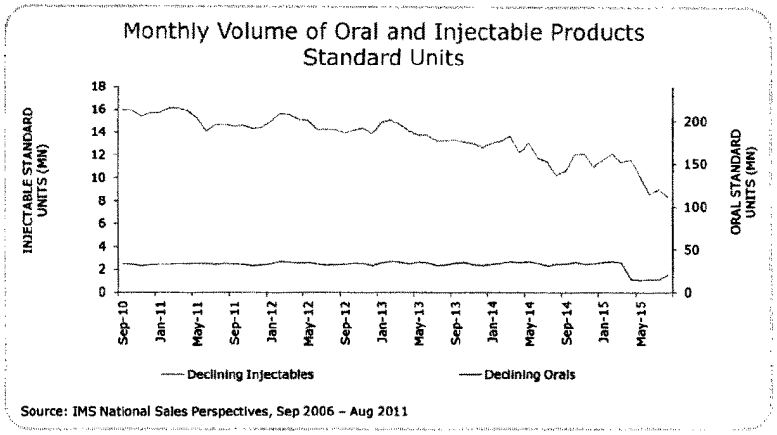
(An additional 6 products were introduced during the 5-year period and not included in the above segmentation.)

In aggregate the declining segment of 75 products have seen monthly supply fall about 47 percent over the 5-year period. For the injectable products, average monthly volume has fallen from 16 million to 8 million standard units for month (Exhibit 6). Included in this segment are 12 oncology drugs, 11 anti-infectives, and 12 cardiovascular drugs, among others.

Exhibit 6

VOLUME AND SALES OF PRODUCTS

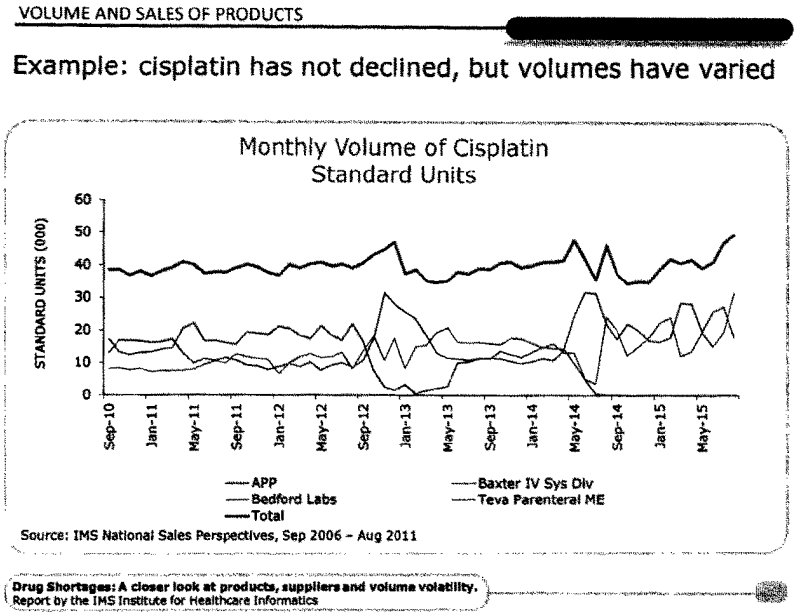
In the declining segment, volume has fallen substantially



Drug Shortages: A closer look at products, suppliers and volume volatility.
Report by the IMS Institute for Healthcare Informatics

For the remaining 55 percent of products in the stable or growing segments, the total volume has not declined, but there may be volatility among the suppliers of the individual products. For example, cisplatin—a widely used platinum-based alkylating agent used in treating about 85,000 patients for a variety of cancer treatments in the past year—has had some volatility in total monthly supply volume, but overall shows a growing volume trend over time. However, a significant level of volatility in supply at the individual company level is evident, including the discontinuation of production in mid-2010 by one company that had been the leading supplier of cisplatin in the 2007–8 period (Exhibit 7). This level of volatility reflects disruption throughout the supply chain which ultimately affects providers and patients.

Exhibit 7

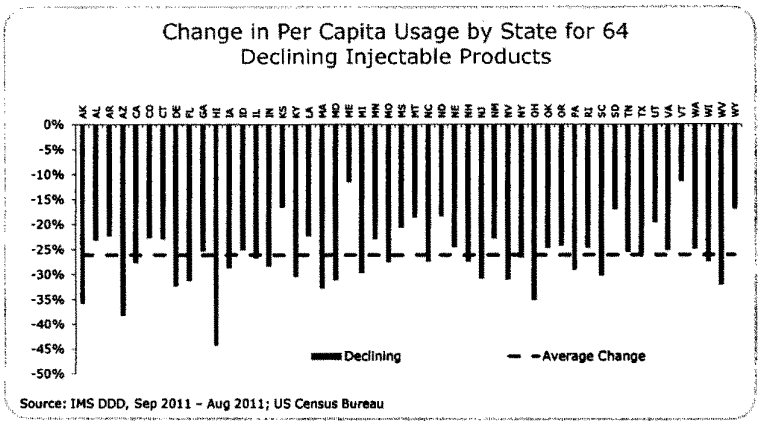


Across the 50 States we see varying levels of volatility in the supply of products on the shortage list. For example, for the 64 injectable products included in the declining segment, the average decline in monthly per capita use between the 12 months ending August 2010 and the 3 months ending August 2011 was 26 percent. Between the two time periods, 13 States had declines in excess of 30 percent suggesting a significant disruption to patient care in a short time period (Exhibit 8).

Exhibit 8

VOLUME AND SALES OF PRODUCTS

The per capita change also varies significantly nationally



Drug Shortages: A closer look at products, suppliers and volume volatility.
Report by the IMS Institute for Healthcare Informatics

RECOMMENDATIONS

Our analysis provides new insights—based on granular information—about the characterization of the products on current drug shortages lists, the suppliers of those products and a deeper, industry-wide understanding of the volume dynamics and volatility for individual molecules and suppliers of those molecules. Our perspective on recommendations is focused on how existing information and analytical approaches can be applied to preventing or alleviating the affects of shortages going forward. Specifically, we believe that an Early Warning System for drug shortages created by the FDA or the industry can be a critical tool to help the regulator, pharmacists and other stakeholders predict, monitor or mitigate the impact of supply disruptions on the healthcare system.

Specifically, the Early Warning system should include the following elements:

1. **Risk Identification:** Systematically identify the high-risk sectors of the generics market. Identify all the low-cost, technically challenging and critical medicines—whether or not they are currently on shortage lists.
2. **Demand Forecasting:** Continuously forecast the long-term demand for low-cost, technically challenging and critical medicines. Adjust forecasts based on such factors as demand trends, new medications, changes in clinical guidelines, practice patterns, care delivery changes and needs of clinical trials.
3. **Volatility Index:** A quantitative measure to systematically track and report month-to-month changes in the volume of drugs supplied to hospitals, clinics and retail pharmacies. Volatility in supply—whether national, regional, by individual supplier, or for specific drug molecules—is a sentinel of problems in meeting demand and instability or dramatic change in the supply chain. Volatility itself can seriously exacerbate problems in meeting demand, encourage overstocking, disrupt patient therapies and facilitate short-term price manipulation by a few suppliers.
4. **Predictive Modeling:** With the wealth of data available, predictive modeling techniques could be applied to anticipate shortages or supply disruptions for critically important medications at the national and regional levels. As data accumulate and measures are improved, the model can tightly focus interventions on those specific parts of the market and supply chain genuinely needing attention.

Other tools would augment the Early Warning System, including self-reporting of demand and supply disruptions by pharmacies, wholesalers, group purchasing organizations and drug manufacturers.

Other tools and mechanisms are needed to augment the Early Warning System, including self-reporting of demand and supply disruptions by pharmacies, wholesalers, group purchasing organizations and drug manufacturers.

We are grateful for the opportunity to present our perspective to this committee and look forward to discussion of the potential solutions.

The CHAIRMAN. Thank you, Mr. Aitken.

Mr. Neas, welcome back to the committee.

STATEMENT OF RALPH G. NEAS, J.D., CHIEF EXECUTIVE OFFICER, GENERIC PHARMACEUTICAL ASSOCIATION, WASHINGTON, DC

Mr. NEAS. Thank you, Mr. Chairman, and thanks, every member of the committee. We are very grateful for your focus on the issue of drug shortages. I am Ralph G. Neas, and I'm president and CEO of the Generic Pharmaceutical Association. GPhA represents the manufacturers and distributors of finished-dose generic pharmaceuticals, bulk pharmaceutical chemicals, and suppliers to the generic industry. At its core, GPhA's purpose is to improve the lives of consumers by providing timely access to affordable pharmaceuticals.

The shortage of critical drugs is a complex, multifactor problem involving many stakeholders. However, much of the shortage problem could be solved by improving the information available both from and to the various stakeholders. These stakeholders would include drug manufacturers, wholesalers, distributors, group purchasing organizations, the FDA, the DEA, and possibly others.

Today, we propose the creation of an accelerated recovery initiative, or ARI. ARI would utilize an independent third party, or ITP, as an unprecedented information clearinghouse to collect information regarding the aggregated available supply of critical drugs, in essence establishing a consolidated supply schedule, and then to use this information to identify potential gaps in supply compared to market requirements.

Upon the acceptance of ARI by both the FTC and HHS, the initiative's mission would be to increase early visibility and communication between the FDA and industry relating to both current and potential drug shortages. Of course, the ITP would be gathering and disseminating information in compliance with all current market regulations and only under terms of strict confidentiality. Efforts would be focused exclusively on critical products where a shortage is expected to last longer than 90 days, and the initiative would operate in a way that would neither restrict competition nor cost taxpayers money.

There can be no question that generic manufacturers are in the business of supplying medicine and ensuring that consumers and patients have access to the drugs they need. Contrary to some media reports, shortages are typically not caused by a manufacturer's decision to voluntarily discontinue supplying the product. Indeed, manufacturers do not and would never deliberately reduce the supply of essential medicines to push prices up.

However, without sufficient information, our efforts sometimes can be misplaced. As one manufacturer put it, we try, but without

knowing more, we occasionally end up over-solving one shortage while under-solving another. The FDA, working with industry through ARI, can help prevent this from happening. Indeed, ARI will allow the FDA and the industry to ensure that limited resources are aimed at the highest priority needs.

This is how the initiative would work. A list of critical products will be determined, incorporating data from multiple sources. With respect to these products, industry will share information with the ITP regarding both available and future supply. The ITP will aggregate this data and communicate where gaps in critical products are found. Based on this information, individual manufacturers will indicate to the ITP how they each could address the shortage.

This feedback loop would continue to help focus industry efforts for the most critical products on the list. As a result, manufacturers will be able to focus their production with a clear understanding of which shortages are being addressed and which are not. ARI will provide greater clarity to available supply of the list of drugs, as well as projected timelines for recovery.

In addition to the initiative I've just outlined, GPhA believes that a recovery from this crisis could be further accelerated through creating a high-level team at the FDA. This team would enable decisionmakers from across the agency and manufacturers to devise strategies to address or avert critical shortages. We've come to think of this, and have shared with the FDA and with HHS, as an FDA SWAT team which could work with industry to make sure listed products are making it to the market.

To be clear, this is not a criticism of the FDA. To the contrary, GPhA applauds the FDA's efforts to ensure that the U.S. drug supply remains the safest in the world. This recommendation is based on the recognition that regulatory efforts sometimes can have the unintended consequence of disrupting the supply of critical products. In fact, as we examine the current crisis, more than half of the shortages have stemmed from regulatory concerns. However, simply by using this SWAT team approach, we believe that the FDA could greatly minimize these unintended consequences without compromising safety in any way.

GPhA is committed to working with this committee, the FDA, the DEA, and all stakeholders to minimize current drug shortages and prevent future shortages from occurring. Nothing is more important to our industry than providing patients access to their lifesaving generic medications. With an intense and timely multistakeholder collaboration, we believe we can accomplish this goal.

Thank you, Mr. Chair.

[The prepared statement of Mr. Neas follows:]

PREPARED STATEMENT OF RALPH G. NEAS, J.D.

SUMMARY

I am Ralph G. Neas, President and CEO of the Generic Pharmaceutical Association, which 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.

Before examining how best to respond to drug shortages it is important to understand that this is a complex, multi-faceted issue and the generic industry has, and will continue, to work tirelessly to be part of the solution. Causal factors of drug shortages are numerous and do not apply in every case. They include everything

from challenges in manufacturing and 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.

A group of generic manufacturers, including both GPhA and non-GPhA members, that represent approximately 80 percent of the generic sterile injectable products sold in the United States, are proposing to take unprecedented steps to build tools and practices that are specifically designed to accelerate the recovery of critical drugs in short supply.

Under this recommended proposal, known as the **Accelerated Recovery Initiative (ARI)**:

• An independent third party will gather current and future supply information from stakeholders for products identified as meeting the critical criteria;
• This will then be used to determine current and potential supply gaps, with a focus on those products where a shortage is expected to last longer than 90 days;
• FDA Drug Shortage staff will be updated when assistance is needed to facilitate production of a product in shortage; and
• A high-level team will be formed within FDA with the ability to quickly respond to critical shortages.

ARI is predicated on voluntary communication between an independent third party and stakeholders involved in the manufacturing and distribution of generic injectable drugs in shortage, including, but not limited to: manufacturers, wholesalers, distributors, Group Purchasing Organizations (GPO's) and the FDA. In addition, this multi-stakeholder approach will provide additional information focusing on real-time decisions and actions proposed by regulatory agencies and their potential impact on critical supply.

This initiative will maintain robust competition, and will not in any way deal with pricing information. It will also require prior acceptance by the Federal Trade Commission and the Department of Health and Human Services. The type of information gathered and disseminated will increase early visibility and communication between the FDA and industry relating to current and potential drug shortages.

ARI also focuses on FDA. The agency deserves tremendous credit for the work it is currently doing to expedite regulatory reviews and work closely with manufacturers. However, there is still more that must be done, and manufacturers would be aided by a formal process specifically designed to facilitate communications related to drug shortage regulatory issues. The industry strongly encourages the establishment of a high-level FDA drug shortage management team, which would include representation from key agency offices. This team would provide an avenue for timely access to FDA decisionmakers by the pharmaceutical industry to review strategies for addressing or averting drug shortages. This high-level FDA team would also be empowered to evaluate issues such as expediting reviews of pending supplements, which enable industry to address shortages of critical drug products.

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.

Good morning Chairman Harkin, Ranking Member Enzi and Members of the Senate Committee on Health, Education, Labor, and Pensions. Thank you for asking me to participate in this very timely and important hearing.

I am Ralph G. Neas, President and CEO of 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 United States, 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.

GPhA is the third major coalition that I have had the privilege of leading. For 15 years, I served as the executive director of the Leadership Conference on Civil and Human Rights, a 60-year-old coalition of nearly 200 organizations that is the legislative arm of the civil rights movement.

For the past several years, I was the President and CEO of the National Coalition on Health Care, the Nation's oldest and most diverse health care reform coalition. The 80 organizations that make up NCHC represent consumers, health care providers, large and small businesses, unions, older Americans, medical societies, minorities, pension funds, religious denominations and people with disabilities.

Personally, I am strongly committed to the perspective of patients. I came down with Guillain-Barre Syndrome (GBS) 32 years ago, an often serious neurologic disorder, usually reversible, that kept me in the hospital for 155 days. More than half of those days were spent in the intensive care unit unable to speak, on a respirator, and totally paralyzed. That harrowing experience led me to help found the GBS Syndrome Foundation International, which now represents 35,000 former GBS patients. In October, we celebrated our 30th Anniversary. With these experiences in mind, I am proud to be here today representing GPhA and I am equally proud of the work our member companies are doing to resolve drug shortages.

INTRODUCTION

I would like to begin today 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 critical drugs. Drug shortages represent a complex, multi-faceted issue and our industry has, and will continue, to work tirelessly 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, drug 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. There can be no question that generic manufacturers are in the business of supplying medicine and assuring that consumers and patients have access to the drugs they need.

Causal factors of drug shortages, 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.

GPhA also acknowledges that while factors contributing to drug shortages are many and complex, roughly half of the reported shortages have been attributed to problems associated with the manufacturing and release of generic sterile injectable products. The manufacturing community has been responsive to this issue and has been extremely active in working with all stakeholders, and especially the FDA, to find suitable solutions that accelerate the availability of critical drugs in short supply. GPhA and our member companies have spent months working with both policymakers and manufacturers to develop strategies to alleviate shortages and better collaborate with other stakeholders.

I have also paid close attention to recent congressional hearings examining the economics of drug shortages and potential economic incentives. I am pleased to see that new and innovative ideas to address the problem of drug shortages continue to be discussed by the Congress. After speaking to GPhA's membership, our member companies have indicated that improved communication, an expedited process for qualifying alternative suppliers and increased collaboration among stakeholders would address the causes of the vast majority of shortages.

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 effectively at all stages of the process. Otherwise, these efforts may have the unintended consequence of adversely affecting our country's supply of critical drugs. Indeed, more than half of the current drug shortages have stemmed from regulatory concerns.

One way to avoid such unintended consequences is by implementing processes whereby remedial measures could be implemented without completely disrupting the manufacturing of necessary products. Through additional remedial measures, the FDA could maintain its vigilance over the safety of the U.S. drug supply, while still ensuring that patients are receiving the medication they need. It is critical that the FDA and 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

Another important factor to note is that the pharmaceutical marketplace overseen by the FDA today is one that has become increasingly 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 United States 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 only have 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 within a much shorter timeframe.

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.

COLLABORATION AMONG STAKEHOLDERS IS NEEDED

We believe these changes would provide a strong start toward reversing the drug shortages currently afflicting patients and preventing further ones from occurring. But as an industry whose entire business model is to make quality medicines available and affordable to all, we are acutely aware that a lack of supply of a critical drug can be devastating, even if it impacts only one patient. Despite all of the 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.

With this in mind, the generic pharmaceutical industry has spearheaded the development of an unprecedented multi-stakeholder communication tool, which we believe will accelerate the recovery of critical drugs in short supply to patients in need. This database of information, which we have labeled the Accelerated Recovery Initiative, or ARI, can be utilized by all stakeholders involved in the manufacturing and distribution of vulnerable drugs in shortage—including, but not limited to manufacturers, wholesalers, distributors, Group Purchasing Organizations (GPO's) and the FDA—in order to accelerate the recovery of critical drugs in short supply to patients in need. In addition, this multi-stakeholder approach will provide additional information to focus on decisions and actions proposed by regulatory agencies and their potential impact on critical supply. Let me provide some more details.

ACCELERATED RECOVERY INITIATIVE (ARI)

A group of generic manufacturers, including both members of GPhA and nonmembers, representing approximately 80 percent of the generic sterile injectable products sold in the United States today, are proposing to take unprecedented steps to establish tools and practices that are specifically designed to accelerate the recovery of critical drugs in short supply. The goal of ARI is to put in place industry practices that provide a more accurate, timely and comprehensive view of the current drug shortage situation, provide greater visibility to shortages and establish practices that allow for potential, voluntary production adjustments to lessen or eliminate the impact of a current shortage. Given the nearly 200 products currently identified by the FDA Drug Shortage staff, the initial scope of the initiative will focus only on those products deemed most critical, which currently focuses exclusively on sterile generic injectable products. We will continue to fine tune the inclusion criteria with a focus on products that have few manufacturing options and no therapeutic alternative.

As I noted, this initiative is predicated on voluntary communication between an independent third party and stakeholders involved in the manufacturing and dis-

tribution of generic injectable drugs in shortage, including, but not limited to: manufacturers, wholesalers, distributors, Group Purchasing Organizations (GPO's) and the FDA. In addition, this multi-stakeholder approach will provide additional information focusing on real time decisions and actions proposed by regulatory agencies and their potential impact on critical supply.

In order for this type of initiative to work, each stakeholder involved in the manufacture, supply and distribution of critical drugs in shortage that is willing to participate will communicate necessary information to the FDA Drug Shortage staff. Safeguards will be put in place to ensure that market and manufacturing information is treated with appropriate care.

Further, this initiative will not limit or restrict competition, and will not in any way deal with pricing information. It will also require prior acceptance by the Federal Trade Commission and the Department of Health and Human Services.

The primary focus of the ARI is to gather the current and future supply information from stakeholders for those products identified as meeting the critical criteria. This will then be used to determine current and potential supply gaps, with a focus on those products where a shortage is expected to last longer than 90 days. This type of information will increase early visibility and communication between the FDA and industry relating to current and potential drug shortages.

The supply information will be gathered and disseminated by an impartial third party in compliance with all current market regulations and under terms of strict confidentiality. This independent third party will be supplied with data related to drugs currently in shortage or expected to go into shortage, including the name of the drug, the expected duration of the shortage and internal reviews to identify production capabilities to respond to any market shortage. Wholesalers and distributors will also supply product availability data to assure a complete review of all available inventories. The independent third party will then aggregate the data to provide an overall view of the projected available supply by product, as defined by critical product criteria, compared to the total market need. If the data reveals gaps in market supply that require FDA intervention, the information will be provided by the independent third party to the FDA Drug Shortage staff so that they may help to develop solutions with the manufacturers.

In addition, wholesalers, distributors, distribution partners and GPO's also have an important role to play. It is necessary for both wholesalers and GPO's to establish a "critical drug supply program" that will be implemented during the time when a drug in shortage is in a supply recovery period. A supply recovery period is the time in which a product is in shortage and has not returned to market demand levels. The focus of the program will be to assure that timely and accurate information is readily available to all affiliated members, institutions and customers.

The last step of ARI focuses on FDA. The agency deserves tremendous credit for the work it is currently doing to expedite regulatory reviews and work closely with manufacturers. However, there is still more that must be done, and manufacturers would be aided by a formal process specifically designed to facilitate communications related to drug shortage regulatory issues. The formation of a FDA drug shortage management team could more effectively address current drug shortages and minimize future shortage events. The industry strongly encourages the establishment of a high-level FDA drug shortage management team, which would include representation from key agency offices. This team would provide an avenue for timely access to FDA decisionmakers by the pharmaceutical industry to review strategies for addressing or averting drug shortages. This high-level FDA team would also be empowered to evaluate issues such as expediting reviews of pending supplements, which enable industry to address shortages of critical drug products.

From an industry perspective, the formation of such a team that includes high-level representatives from the FDA's Center for Drug Evaluation and Research medical staff, Office of Compliance, Drug Shortage staff and Office of Regulatory Affairs could provide the expertise and the appropriate level of authority to effectuate rapid decisions on steps to address drug shortages.

We recommend that industry work with FDA and other stakeholders to implement the ARI communication tool in parallel with our other recommendations in order to increase the channels of communication and strengthen our collective ability to supply patients with the medicines they critically need.

CONCLUSION

In conclusion, Mr. 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 the lifesaving generic medications they require, and with a joint ef-

fort among all involved, we believe we can make a significant step toward accomplishing this goal.

The CHAIRMAN. Thank you very much, Mr. Neas.

And now, Dr. Maris, if you'll sum up, I'd appreciate that. Please proceed.

STATEMENT OF JOHN M. MARIS, M.D., CHIEF, DIVISION OF ONCOLOGY, CHILDREN'S HOSPITAL OF PHILADELPHIA, PA

Dr. MARIS. Mr. Chairman, Senators, ladies and gentlemen, thank you for the opportunity to speak to this panel today, and I'd like to take this opportunity to thank Senator Casey for his very kind introduction. Senator Casey has been a firm advocate for children, a leader in this area, and with Senator Klobuchar, the legislation before us and the eloquent discussion today, we're very encouraged that there's movement, and we look forward to this committee's role in reaching solutions.

Today I'd like to speak to you as a pediatrician, as an oncologist, and also as a cancer researcher, to really cover three points in my 5 minutes. I'd like to talk to you about how our organization, the Children's Hospital of Philadelphia, has responded to this crisis. I would like to talk to you as an oncologist and how this has affected me and my practice and the patients that I serve. And I'd also like to spend a brief minute talking about something that hasn't been discussed here that much, how this is affecting something that we in this country should be so proud of, which is our clinical research enterprise and how this is impacting dramatically clinical trials and making advancements.

I think I speak for all of us in the field when I say that sitting here today we feel like we've dodged a bullet to date. We feel that there is this impending sense that if the status quo remains or there aren't substantive solutions really soon, that we are going to see unintended consequences of this.

As far as I know, there's not a reportable death, yet, that's directly linked to drug shortage, but in my opinion it's just a matter of time, and that's why I'm very hopeful that this committee—and I sense the urgency here—will really address this and address this quickly so that our patients will be protected.

The Children's Hospital of Philadelphia is the largest pediatric health care organization in the Nation. Over a million patients walk through our doors each year. And we've invested heavily in this problem. It was interesting to hear how many staff there are at the FDA. At CHOP we've needed to have three full-time people work on this problem. We have three individuals who do nothing else but deal with the drug shortage issue.

We've had to get innovative. We had to purchase infrastructure to, believe it or not—we're talking about sterile injectables. These are solutions that come in small vials. We have robotics now that can take these solutions out, actually preserve every last drop of it so that we can get this out to our small patients and really be as efficient as we can. And we have an intensive monitoring system. And I can tell you that as I sit here today, these are just data from today, that there are 35 drugs that we use every day that we only have knowledge that we'll be able to have for the next 4 to 8 weeks, 9 drugs with 2 to 4 weeks supply, 10 drugs with less than

2 weeks supply, and there are 8 drugs that we commonly use at Children's Hospital that we don't have right now. And these are important drugs.

To be clear, what we've put into place at CHOP is possible because of the resources we have, the intellectual resources, but it's not sustainable and it's probably not replicatable by many places across the Nation.

We've heard some anecdotes, and Senator Klobuchar opened with a child with leukemia, and indeed let me just tell you briefly what happened last summer. Despite everything we had in place at CHOP, there was a 6-week period where we could not get a drug called daunorubicin. We've heard doxorubicin mentioned here today. There's another medicine called daunorubicin. We could get the doxo, and we had met and talked about this issue, and we needed to substitute it.

Just imagine for a minute that you're a parent or a grandparent and you're sitting in a room with a physician who is giving you the news that your child or grandchild has cancer, and that we have researched this over the years and we've figured out a solution that's going to work most of the time. But one of the drugs, one of the key essential ingredients, we don't have.

And so we're going to come up with a Plan B. And, no, we have not been able to research this plan. And, no, there's really not evidence that it's going to work as well. But that's what we've needed to do, and we've needed to do it repeatedly.

In this particular situation, doxo, which we thought should be a good replacement for dauno, it's too early to know whether these patients will relapse and whether it impacted, but it definitely made them more sick. Children got mouth sores, got infections, spent time in the ICU. No child died from this, but there was no doubt it was the unintended consequence of serious toxicity due to this substitution.

You have to understand that cancer care at a place like CHOP is very complex, dozens of therapies at the same time, an electronic health record that has hundreds and hundreds of treatment protocols. So just replacing a drug is something that is subject to human error and is a very time-consuming and inefficient process that we need to get beyond.

My last point is that each of the children over the summer and most of the children treated in pediatric health care institutions for cancer are on clinical trials, and there's no doubt that we still don't have a sense of how these changes to the backbone of chemotherapy in clinical trials is going to affect our understanding of how to move the field forward.

I think it's also very important to emphasize that there is a lot of excitement about developing new drugs, new therapies for cancer, and that's the sort of work that I do. But there is an unrealistic assumption that they're going to replace these drugs that we're talking about today, and that's not true at all. The new drugs are built on the backbone. Cancer research is incremental, and it's very frustrating to me to have these new drugs, some of which we've developed, and we're ready to move them into clinical trials, but we can't even use the backbone that we're going to need to

build on. And so this is an incredibly important part of the debate that I think has not been discussed here in detail today.

Mr. Chairman, I'm very pleased to be part of this process and to give the frontline view of what we see as a critical problem. I've been there in the room looking a family in the eye to tell them we don't have a drug, and this is something that I look to this committee and members of the panel to find solutions as quickly as possible. Thank you.

[The prepared statement of Dr. Maris follows:]

PREPARED STATEMENT OF JOHN M. MARIS, M.D.

My name is Dr. John Maris, Chief of the Division of Oncology at The Children's Hospital of Philadelphia (CHOP) and Director of our research institute's Center for Childhood Cancer Research. CHOP is the Nation's largest pediatric healthcare network with over 50 locations throughout Pennsylvania and New Jersey and has over 1 million patient encounters each year, which requires significant need for generic drugs that are relatively common and orphan drugs that are not widely used because of the high acuity and specialized nature of many of our patients.

We are concerned with the inadequate supply of life-saving cancer drugs used in my pediatric oncology patients, anesthetics used during surgery, and a large number of "sterile injectables" used by our neonatologists in many of our most vulnerable patients. In response, CHOP's pharmacy developed a customized database that provides real-time information on our day-to-day supplies. The number of drugs in short supply at our hospital has been steadily increasing. In fact, there are eight drugs that we have completely run out of, forcing us to substitute potentially equally effective, but often less desirable, replacements.

For example, CHOP was unable to obtain daunorubicin, a drug known to be essential for the cure of childhood leukemias—the most common pediatric malignancy—and part of our standard of care for over two decades. We were then forced to use the drug doxorubicin as a replacement, despite there being no data available on the safety and effectiveness of this as a leukemia therapy or any other replacement. Withholding the drug altogether would definitely result in a much higher risk for relapse. While it is too soon to know if the substitution impacted the curability of these children, we noted significantly more side effects, mainly severe mouth and gut ulcerations, fever and infections. While no child died from these complications, it is my opinion that it is only a matter of time before this type of tragedy will occur. Absence of a single drug requires us to rewrite the formulary and road maps for each patient who may receive a substitution, a procedure which is highly complex, resource intensive, and frankly highly subject to human error. Further, each of the children who received the substitution over the summer were in the midst of a clinical trial and we are deeply concerned that these types of deviations from accepted practice will impact NCI-sponsored clinical trial results.

While in most cases we are able to address such challenges in our pharmacy, I suggest that any solution involve a partnership between providers, manufacturers and government. This begins by making sure that information on impending shortages is delivered responsibly and in real time because the lack of notice of a medication becoming unavailable can put patients at significant risk since many times there are not appropriate alternative therapies for critically ill children, or those with rare diseases. Other critical information we need is an accurate estimate of resupply dates so that we can accurately determine the most appropriate conservation practices. Abolishing "gray market" practices would also help assure patient safety, maximize legitimate supplies, and keep healthcare costs down.

It is important to note that the NCI infrastructure has supported major advancements in recent years in the development of completely new and impactful treatments to cancer. However, each of these advances is built on the backbone of existing therapies, almost all of which are off patent at this time. Without the bedrock of established and curative drugs, recent discoveries mean many of our most seminal advances in the field are in jeopardy of being reversed due to this issue. Tools that help doctors provide excellent patient care need to be readily available and continuously improved and these include pharmaceuticals. We must remember at the epicenter of this issue is the patient and I hope the information I shared will further invigorate your efforts to ensure that drugs are readily available for the people that depend upon them most.

Good morning. My name is Dr. John Maris, Chief of the Division of Oncology at The Children's Hospital of Philadelphia and Director of our research institute's Center for Childhood Cancer Research. In addition, I am a Professor of Pediatrics at the University of Pennsylvania where I direct the Pediatric Oncology Program in our National Cancer Institute funded comprehensive cancer center.

I thank Chairman Tom Harkin and Senator Mike Enzi for holding this hearing today, in addition to Senator Bob Casey, Jr. who has made this and other issues impacting the lives of children a high priority.

The Children's Hospital of Philadelphia, or CHOP as it is more widely known, is the Nation's largest pediatric healthcare network with over 50 locations throughout Pennsylvania and New Jersey. We have over 1 million patient encounters each year and are home to one of the largest pediatric research programs in the country. CHOP shares the highest ranking on U.S. News & World Report's Honor Roll of the Nation's best children's hospitals. Our main hospital in West Philadelphia provides tertiary and quaternary care to a number of children having multiple chronic conditions or who are affected by rare pediatric diseases. Because of our high volume, we have an expansive need for generic drugs that are relatively common but we also utilize orphan drugs that are not widely used because of the high acuity and specialized nature of many of our patients.

As a physician focused on childhood cancer, my top priority is to make sure patients receive the best and safest care possible. As a researcher, I am dedicated to finding cures for cancer while minimizing or eliminating any side effects that result from the treatments we provide to this very vulnerable group of children. Both roles have enabled our research team to identify the main genes associated with neuroblastoma, an extremely aggressive form of childhood cancer. As a result, we have moved some of these discoveries toward new therapies, a number of which are now in clinical trials and we certainly hope will someday lead to a cure.

We work relentlessly to overcome obstacles in our work. The drug shortage we discuss today is one that has had a very potent impact on the progress we strive to make in research and clinical care. It slows down our progress and can even bring it to a grinding halt. Institutions like CHOP, and the National Institutes of Health, have invested significant resources towards translational research, where we convert our progress in the labs into treatments that may save lives in the hospital. However, without the drugs that are known to provide cures and form the backbone of our armamentarium, an important link in this chain is missing which can cause setbacks of epic proportions.

My goal in this testimony is to provide insight into our concerns at CHOP and share with you how we have responded to the drug shortages. I will close with some of my personal opinions on suggested solutions with the hope that they may help the committee in its efforts to address this pressing issue.

Beginning with our more broad concerns, I will tell you that there are a number of drugs we use commonly that are either in short supply or not available. These include life-saving cancer drugs used in my pediatric oncology patients, anesthetics used during surgery, and a large number of "sterile injectables" used by our neonatologists in many of our youngest and most vulnerable patients. In response to these shortages, CHOP's pharmacy developed a customized database that provides real-time information on our day-to-day supplies. The number of drugs in short supply at our hospital has been steadily increasing over the last few years to 123 drugs today, most of which are generic injectables. We are monitoring 35 drugs with a 4 to 8 week's supply; 9 drugs with a 2 to 4 week's supply; and, 10 drugs with less than 2 week's supply left. There are also eight drugs that we have completely run out of, forcing us to substitute potentially equally effective, but often less desirable, replacements.

This list includes:

- mitomycin injection, which is used for some surgical and ophthalmic procedures;
- co-trimoxazole (Bactrim) injection (which is available on a compassionate use basis), but a commonly used antibiotic to prevent serious infections in patients with compromised immune systems;
- diazepam (Valium) injection, which is used as a sedative in surgery and for seriously ill patients;
- pancuronium injection, which is used to immobilize patients for surgery;
- ammonium chloride injection which is used to alter the acid/base balance in critically ill patients; and
- Selenium, chromium and cysteine injections, which are all used to feed patients intravenously. The shortage of these agents poses a particularly dire situation for patients, often the neonatal population, who are unable to be fed in any other manner.

All of these shortages are presenting significant challenges to our medical staff and can have life-threatening consequences for our patients.

I would like to provide a recent example of how the drug shortage problem directly and seriously impacts children with cancer at CHOP, and how the consequences have a potentially dire impact in both the short- and long-term. For a 6-week period this past summer, CHOP was unable to obtain daunorubicin, a drug known to be essential for the cure of childhood leukemias—the most common pediatric malignancy—and part of our standard of care for over two decades. This drug is a big part of why we can offer curative approaches to the majority of patients. We were forced to use the drug doxorubicin as a replacement, despite there being no data available on the safety and effectiveness of this as a leukemia therapy or any other replacement. We did know, however, that withholding the drug altogether would definitely result in a much higher risk for relapse. While it is too soon to know if the substitution impacted the curability of these children, we noted significantly more side effects, mainly severe mouth and gut ulcerations, fever and infections. While no child died from these complications, it is my opinion that it is only a matter of time before this type of tragedy will occur. You must understand that delivery of cancer care to children requires a highly complex infrastructure. At any one time, we have about 50 children receiving chemotherapy at CHOP and there are over 300 different cancer treatment road maps written into our electronic health record. Absence of a single drug requires us to rewrite the formulary and road maps for each patient who may receive a substitution, a procedure that is highly complex, resource intensive, and frankly highly subject to human error. Finally, each of the children who received the substitution over the summer were in the midst of a clinical trial, and we are deeply concerned that these types of deviations from accepted practice will impact NCI-sponsored clinical trial results.

Another shortage we're experiencing here at CHOP includes some ingredients used in total parenteral nutrition (TPN), which is a way of supplying all the nutritional needs of the body by bypassing the digestive system and dripping a nutrient solution directly into a vein. The intravenous compound consists of carbohydrates, protein, fat, multivitamins, and numerous electrolytes and minerals essential to sustain life in patients unable to ingest food by other means. Approximately 50 percent of the patients admitted to CHOP's neonatal intensive care unit (NICU) have conditions such as gastrointestinal abnormalities and/or extreme prematurity, which require TPN to survive. CHOP often finds that many of the ingredients essential to TPN are either completely unavailable or on shortage. For some of these ingredients, such as selenium (which is one of the injectables that we are completely out of), there is no substitution. For others, including sodium phosphate, there are alternative agents, but these alternative agents contain other ingredients (like aluminum) that may be harmful to patients, resulting in neurotoxicity or renal failure. The inability to provide appropriate TPN to patients may result in inappropriate nutrition, leading to electrolyte abnormalities, negative developmental outcomes (cognitive and physical), and longer hospitalizations. In order to prevent these complications, physicians, pharmacy and nutrition staff must invest a significant amount of time to develop an appropriate substitution, often limited to oral supplements. However, many children cannot take these due to their illness, leaving their families and doctors with no alternative. The only solution to this problem is the return of the electrolytes and trace elements in shortage, the major components of TPN, back to the market.

In most cases, we are able to address such challenges in our pharmacy. On a daily basis, our pharmacy purchasing staff monitors the availability of medications known to be in short supply nationally and enters this information into a customized database for tracking purposes. The Pharmacy has a weekly meeting of key personnel (supervisors, managers and clinical pharmacists) to review each shortage individually, update the status, and create a contingency plan for ongoing issues. Key physicians are contacted regarding shortages that may affect their patient population and plans for conservation and alternative therapies are created and implemented, often on an emergent basis, as there is often no notice that a medication is about to become unavailable. Conservation measures may require significant effort on the pharmacy department, in terms of re-distributing supplies, repackaging large quantities into smaller quantities, and tracking prescribers down to change orders. We have invested over $2 million by purchasing two "robots" which allow us to more efficiently use and repackage medications that we buy in large quantities. This allows us to stretch our supply and use every drop of a particular drug. The Hospital's response is designed to help us avert disruptions in patient care while ensuring the safety of our patients. These resources represent a significant financial investment, but help us mitigate the impact of drug shortages here at CHOP. All of these processes take a minimum of three full-time CHOP pharmacy staff persons.

While these efforts have helped us address these challenges, we have not overcome them entirely. I suggest this requires a partnership between providers, manufacturers and government. This begins by making sure that information on impending shortages is delivered responsibly and in real time. S. 296, legislation introduced by Senators Amy Klobuchar and Casey, coupled with President Barack Obama's Executive order, will require drugmakers to notify the Food and Drug Administration of shortages and this is an important step in the right direction. We need this information because the lack of notice of a medication becoming unavailable can put patients at significant risk, since many times there are not appropriate alternative therapies for some of these critically ill children, or those with rare diseases. Without notice, there is no time to conserve or prepare for a prolonged absence of a routinely used medication. Other critical information we need is an accurate estimate of re-supply dates. These are often a moving timeline that is continually being pushed into the future, without any target date in sight at all. Knowing when a medication will truly become available again would help us determine the most appropriate conservation practices. Abolishing "gray market" practices would also help assure patient safety, maximize legitimate supplies, and keep healthcare costs down.

For me, as someone who spends significant effort developing new therapies for cancer, the paradox is quite striking. The NCI infrastructure has supported major advancements in recent years in the development of completely new and impactful treatments to cancer. However, each of these advances is built on the backbone of existing therapies, almost all of which are off patent at this time. It is quite striking that it is easier for me to get to my patients a drug discovered only recently and with a limited, and sometimes nonexistent, track record of curing children with cancer, but I cannot get them drugs that have been the bedrock of our curative therapies since the 1970's. Modern cancer therapy is not a replacement of the old ways; it is an integration and an enhancement of established curative methods. Without the bedrock of established and curative drugs, recent discoveries mean many of our most seminal advances in the field are in jeopardy of being reversed due to this issue.

I close today by commending this committee for not only investigating the issue, but for also helping to identify a solution for it. While I have shared insight into how The Children's Hospital of Philadelphia is addressing drug shortages, I will tell you that our efforts have required us to be nimble and shift resources away from other priority child health demands, so that we may address this important problem. We have very high standards for patient care and safety and we will not allow this crisis to compromise that. As a pediatric oncologist, I am awestruck at how such an issue can so dramatically impact the children afflicted with cancer and the research infrastructure we have built over decades to arrive at curative therapy for all. As standards continue to rise, as they should, the tools that help doctors provide excellent patient care need to be readily available and continuously improved. These tools include pharmaceuticals. We must remember at the epicenter of this issue is the patient and I hope the information I shared will further invigorate your efforts to ensure that drugs are readily available for the people that depend upon them the most.

The CHAIRMAN. Thank you, Dr. Maris. Thank all of you. We'll begin a round of 5-minute questions.

One thing that's come through to me from the first panel and from this panel—almost every one of you talk about it—is the need for early warning, early information coming from the manufacturers to FDA. Mr. Neas had the ARI. Mr. Aitken, you talked about an early warning system. I guess those are similar concepts. Dr. Maris, you talked about it in your testimony, too. Dr. Crosse, in your findings, GAO found that.

Somehow FDA is not getting any kind of advanced warning from manufacturers that they may potentially face a shortage. Is that correct?

Ms. CROSSE. Yes.

The CHAIRMAN. OK. But you point out, Dr. Crosse, that FDA does not have the authority to mandate this.

Ms. CROSSE. That's correct. Currently they have a very narrow authority.

The CHAIRMAN. Very narrow authority.

Mr. Neas, maybe this is for you. Would the manufacturers voluntarily enter into some agreement with the FDA to provide upfront information when they expect to see a shortage? As I said earlier, the problem is you get two or three or four manufacturers, and FDA doesn't really know what they're all doing. If they had this reporting in, then FDA could take a look and see and anticipate whether or not there may be a shortage.

But is this something voluntarily that they would do, or does FDA need some more authority to compel this type of information?

Mr. NEAS. Mr. Chairman, many of the generic manufacturers already voluntarily supply that type of information. Having said that, we're working with many members of the Senate and the House looking at these notification bills, and we are working with the members, and we want to make sure there are no unintended consequences, especially with respect to the gray market and violating confidentiality.

We're also thinking that it probably should apply to everyone in the supply chain, not just with respect to manufacturers. There are some really good ideas out there, and we just want to make sure that it's framed precisely so that we can all have multistakeholder support.

The CHAIRMAN. I'd like to know what that precisely is. So we kind of all agree they need this information one way or the other, but then you get to the second problem, Dr. Crosse, which you point out, so what does FDA do with it? They have no authority to tell a manufacturer you've got to produce more or to do something. Then what do you do with that information?

Ms. CROSSE. We found that when FDA did get advance notice, they were able to be pretty effective. In the majority of instances where they knew about a potential shortage, they were able to take steps that were able to prevent that shortage from really becoming the full-blown kind of problem that we're seeing with other drugs. The problem is that right now, the majority of the time they don't know about a problem in advance. They learn about it from hospital pharmacists, from patients, from other systems that are collecting data. FDA is not finding out about it soon enough.

The CHAIRMAN. I still wonder what they do. If they see a shortage coming, they can't go to a manufacturer and say produce more, can they, Mr. Aitken?

Mr. AITKEN. I think here also we need to differentiate the nature of what a shortage is. I think a manufacturer that is anticipating that they will reduce their production of a particular product, that's one type of issue that we've heard talked about.

But shortages exist because demand exceeds supply, and that's why we believe actually you need to factor in the demand forecasting for perhaps a 3- to 5-year period in advance, understand where that incremental capacity can come from, from the various manufacturers. Even if an individual manufacturer may not be reducing their actual supply, there may still be a shortage.

I think, though, this has to be grounded with the manufacturers, but it does have to be multistakeholder. The intermediaries are an important part of this as well.

The CHAIRMAN. Mr. Neas. Dr. Maris.

Mr. NEAS. Mr. Chairman, I do want to re-inforce the accelerated recovery initiative that we're talking about. FDA has so much on its plate, and we're definitely supportive of increasing resources and addressing the crisis.

With respect to looking at the supply schedule, that's why we think this new initiative, this unprecedented private sector, nonprofit initiative where we could actually collect the necessary information and come up with an aggregated available supply of critical drugs and get a consolidated supply schedule, and then use this information to identify potential gaps in supply compared to the current market requirements. We think this is market-based. We think it comes from the industry. We know this is a variable problem, but we want to work with FDA and with everybody in the supply chain.

The CHAIRMAN. Dr. Maris.

Dr. MARIS. In terms of projecting demand, I think that at least in the oncology field, there are decades of data, and I think it's pretty clear what the demand is going to be for most of the sterile injectables for oncology.

In terms of tracking, I mean, what we do at CHOP is we don't just track the manufacturers. We track at multiple points along the supply chain, and I think that's been a critically important part of our being able to stay somewhat ahead of it and knowing more from the supply chain side when there's going to be an impending shortage. The reason why it's so critical is that we can make those alternative plans sooner rather than overnight.

The CHAIRMAN. Thank you all very much. My time has expired.

Senator Merkley.

Senator MERKLEY. Thank you, Mr. Chair.

Dr. Maris, could you comment on the impact that the stress has on patients when patients find out that drugs may not be available when they're in the third course of treatment, or that the drugs may have to be switched to something else and they are not sure if it will work? And in general, whether it makes a difference as to whether a patient is able to focus their mind and heart on healing or has to focus their mind and heart on, wow, am I going to be able to have the drugs available?

Dr. MARIS. Thank you for the question, and I think that the quick answer to your question is it's not measureable, but it's significant. I think that, at least in pediatric oncology, this conversation most often comes up during that incredibly horrific time of diagnosis when there is so much going on in terms of being faced with a child with a life-threatening illness, being faced with a major change in life as families know it, the reality that therapy is on its way, and then to hear that there is a major chink in the armamentarium is devastating. I don't know how to articulate it any better that it is a very significant problem.

Senator MERKLEY. And you noted often this is a time, at the beginning of treatment or diagnosis, but I've talked to a patient, and my impression is it's not that uncommon for it to happen in the middle of a course of treatment as well, first starting with a delay, come in Thursday rather than Tuesday, and then getting calls saying we still don't have the drugs, throwing the whole family into

chaos as to what role should they be playing in trying to track down appropriate drugs.

Dr. MARIS. And there's no doubt that the time of diagnosis is when families are most vulnerable, but during therapy as well. To have a potentially curative therapy withdrawn from being available to you is quite, quite difficult. And a point that I'd really like to make from the physician side of things and the researcher side of things is substitution is, at best, an inexact science.

Senator MERKLEY. And you had noted in your testimony that in some ways a bullet has been dodged because there's not an attributable death. But certainly I have an impression from medical providers in Oregon that whereas there may not be an exact correlation of saying this person died because something was unavailable, that many, many times, almost on a daily basis, shortages are compromising the effectiveness of treatment. Would that be fair to say?

Dr. MARIS. I think it would be not only fair, and I'd like to expand on that by saying that I cannot pick up the medical literature and say this case report directly links drug shortage to a death, but I think all of us in the field feel that it is impacting patient safety and quality care quite dramatically already, and we're just very concerned that this is the tip of the iceberg if we don't do something soon.

Senator MERKLEY. Thank you very much.

Mr. Neas, several of us are trying to get our hands around this gray market. It's clear that when there is something in short supply, there's a temptation to try to gain a supply of it and gain as much as possible, increase the shortage, and then be able to sell at a high profit. We heard testimony earlier about a 100-fold increase.

As I think about the pharmaceutical benefit managers, they're in the business under contract to purchase drugs from the manufacturers, under contract to deliver. Are there some PBMs that appear to be in the business of buying extra amounts, hoarding them, raising prices, or is it the impression that really, no, this would never happen within the official system? We're talking about third-party players who are coming in to try to gain these supplies and then sell them at horrifically increased prices.

Mr. NEAS. Senator, I'm not aware of any incidents within the pharmacy benefit managers. I do want to echo, however, what you have said, and Senator Blumenthal and others. It's truly an outrageous situation. As some of you know, I've just completed my third month as the new CEO. But in my first week, I had a chance to attend the FDA workshop on drug shortages, and there were repeated references to the gray market. But no one could really get a good handle on how much of a problem it was.

My very first question after my presentation when we were in the panel was who has jurisdiction? Who is invested by the law, by Congress? Is it the FTC? Is it Department of Justice? Who has responsibility? I'm not sure any of us have gotten the real response as to the extent of the problem, who is responsible, and who should be investigating and enforcing. I think it's a major issue.

Senator MERKLEY. One doctor told me that his institution refuses to pay these inflated prices. But then families, when the institution can't acquire the drug, are searching the country over the Internet,

so on and so forth, trying to find the drug for their ill family member, and I want to echo what you just said. It's absolutely unacceptable. Certainly I want to work with all my colleagues and work with you all and the industry on how can we stop this drug scalping, which aggravates existing shortages. To me it's absolutely unacceptable. And so I hope to get your help, all of your help, in finding a way to address this.

Yes, doctor?

Dr. MARIS. I just want to add that there's been a lot of discussion about who this gray market is, and I don't know why it's a mystery. I mean, we get faxes every week, and we just shred them. But, I mean, you can have them.

Senator MERKLEY. Thank you. I would appreciate if you could set aside a week's supply, and it appears that there's a gap here as we're hearing the testimony. It seems like there's a gap in terms of no one having accountability. It hasn't become the FDA's role to investigate this and take it on. Apparently, attorneys general haven't taken it on, perhaps because it's not a crime.

But we have to fill this gap, and I think that's a very valuable insight coming out of this committee, and we have to devise a way, if it's not illegal, to make it illegal and to end this practice.

I thank you all very much.

The CHAIRMAN. Thank you, Senator Merkley.

Well, there is a former attorney general who is focused on this. Senator Blumenthal.

Senator BLUMENTHAL. Thank you, Mr. Chairman, and my thanks again for having this hearing and all of your excellent testimony.

Dr. Maris, it may be no mystery, but the problem is there has been no real investigation. That's the very simple answer to a doctor, talking to you as a former attorney general. But as a lawyer, some of these practices are quite clearly against the law, existing law. This kind of anti-competitive misuse of market dominance fit almost a textbook case for an FTC or Department of Justice investigation. And so I would take your comment as further support for it.

Mr. Neas, I first want to thank you for your very distinguished work in the area of consumer protection, as well as civil rights and civil liberties, and welcome your proposal, which I think is helpful in advancing the debate or discussion. Simply to think of a team, a SWAT team as you called it, that would be more proactive and interventionist, aggressive in this area I think is a welcome initiative.

My question to you is whether the FDA really has sufficient authority now to make the SWAT team effective. The concept may be good, but you've heard the GAO report, Dr. Crosse in particular, talk about what the FDA cannot do now. And so I wonder whether your team proposal wouldn't call for more authority on the part of the FDA.

Mr. NEAS. That's a good question, Senator. I'm not sure of the answer. I know something has to happen. We've heard about the backlog and the shortage problem, and the FDA needs so much help. They're so good, but they need so much help, just materials from the Office of Generic Drugs. The median approval time of an abbreviated new drug application is now 30 months for a new drug

application. That's 65 percent higher than 4 years ago. There are now 2,000 abbreviated drug applications that are over 180 days, 2,000, another 600.

They need personnel. They need prioritization. There's got to be more coordination. I think the SWAT team approach—Drug Shortage does an unbelievable job. But we were told we went from three or four to seven or eight, or eight or nine.

When you stated the question about the nature of the crisis, I think the response of the multistakeholder collaboration, its intensity should match or exceed the nature of the crisis. If this is this kind of a crisis, I think eight people at Drug Shortage is far fewer than they need.

And by the way, we have worked with FDA on the PDUFA bill, which will be before you all. And Senator Harkin, Mr. Chairman, we've talked about it one on one. It is going to be an enormously consequential legislative measure, providing 800 or 900 more inspectors with respect to facilities inspections, but it's also going to help with the abbreviated drug problem, the application and approval problem.

But there's got to be that coordinated prioritization. And I'm not saying there's not talk in meetings and prioritization. I think it has to happen on a far higher level with much more intensity and effectiveness.

Senator BLUMENTHAL. I thank you for that answer, and I agree with you on your comments about the staff shortage.

Dr. Crosse, let me ask you, your report says that the drug shortages—and I'm going to quote exactly the line—"65 percent of shortages involve drugs that were in short supply more than once." Does that mean that the same drug was in short supply more than one time; in other words, repeated times? I would read the plain English as saying that.

Ms. CROSSE. Yes, that is what we mean. Many of these drugs have been in short supply multiple times over the last decade. Some of the drugs that we looked at in detail had been in short supply as many as five times.

Senator BLUMENTHAL. It isn't as if there's a short supply, there's a manufacturing problem, the FDA comes in, offers friendly advice, the problem is fixed, no problem again. These are chronic, repeated shortages.

Ms. CROSSE. In some instances, they are. All of the 15 drugs that we looked at in depth, I think there were only four of them that had not been in short supply multiple times across the last decade.

Senator BLUMENTHAL. One last question, and thank you for your great work on this report. You say that, again in the report, that over half—and I'm quoting—"over half of shortages reported during the relevant time period were in generic injectable drugs." As others have commented here, a substantial percentage were not in that category. Do you know the percentage?

Ms. CROSSE. We do have information in the report. I'd have to sit here and add those numbers up, but we do have a figure in the report that lays that out. The injectable drugs that were available only in generic form, 53 percent. An additional 15 percent of injectable drugs were available only in brand name forms. Then there were 16 percent that were orally administered drugs avail-

able in generic form. That could be generic and brand name. And another 4 percent were orally administered drugs available only in brand name form. And then there were 12 percent of other types of drugs that were topicals and other sorts of things.

Senator BLUMENTHAL. I would like to have an opportunity for my staff to contact you and verify those numbers. And also, since I'm out of time, I can't ask this question. But I'm interested in why the FDA does not have sufficient authority now to require notification of a drug shortage under 506(c) of the Federal Food, Drug and Cosmetic Act. I gather it is requiring some kind of notification, and why it does not have sufficient authority now.

Ms. CROSSE. Right. The current authority only relates to where there's a sole supplier of a drug, and that drug has to be life-supporting, life-sustaining, or to prevent a debilitating disease or condition. It's a narrow set of drugs that are covered by the current authority.

Senator BLUMENTHAL. Is that as a matter of regulation?

Ms. CROSSE. That's their statutory authority.

Senator BLUMENTHAL. OK. Thank you very much.

Thank you again to the entire panel. You've been very helpful.

The CHAIRMAN. Senator, I think Mr. Neas wanted to respond to this.

Senator BLUMENTHAL. I'm sorry.

Mr. NEAS. Mr. Chairman, thank you so much. I just need 30 seconds. Is that all right?

The CHAIRMAN. Absolutely.

Mr. NEAS. This accelerated recovery initiative, which is brand new in terms of being announced today, the multistakeholder approach that people have been talking about, I do want you to know that Premiere, one of the group purchasing organizations, has come out for it today, and I believe there could be a number, maybe all of the group purchasing organizations. We've had pharmacists, hospitals, American Cancer Society. I've also met with John Castellani about working together on drug shortages.

I'm just making a point to demonstrate momentum, but most importantly the multistakeholder collaboration within the industry, but also with FDA, with you all, and with the executive branch.

Senator BLUMENTHAL. I would welcome that cooperation as we move forward. Thank you very much.

Thank you, Mr. Chairman. Sorry to go over my time.

The CHAIRMAN. Oh, that's fine, Senator Blumenthal.

Senator Casey.

Senator CASEY. Thank you, Mr. Chairman. I know we're at the end of the hearing, and I apologize for my back and forth here.

The CHAIRMAN. Oh, no. Please.

Senator CASEY. It's been one of those days.

Doctor, and I know our other witnesses—I'll make sure that I submit questions for the record. I'm grateful for your work and the scholarship and the advice that you give to us. But I wanted to start with Dr. Maris, and I'll be rather brief.

I know that Children's Hospital in Philadelphia has invested a tremendous amount of time and resources trying to manage this problem and trying to deal with it directly, and I guess I'd ask you, because I know you've got a technological infrastructure and other

means to help track these shortages, but what advice can you give, if any, that's relevant to a smaller entity, a smaller hospital or hospital system or in a community where they may not have the IT resources, they may not have the opportunity to invest in the way that you have? Any kind of common practices that would prevail, no matter what the level of investment or resources, that you could give us some advice about?

Dr. MARIS. Thank you for that question. I'll answer it two ways. The first answer is that it's very difficult and may not be practical for many smaller institutions to do what we've been able to do. That was one of the points I wanted to get across is that we've been able to address this issue, but many places may not be able to.

In terms of tangibles that we can share, there's no doubt that the grassroots tracking system that we put into place, the databasing, is already being shared amongst the pediatric, the Children's Health Care Association and the major children's hospitals. But how we can trickle that down to all the children's hospitals is something that we have not addressed yet.

Senator CASEY. And we'll try our best to be able to provide that kind of feedback.

One of the main purposes of the legislation that Senator Klobuchar and I and a whole host of others have been working on is to provide that early warning system in place that several of our witnesses today have spoken to, in one kind or another.

I want to make one point for the record. I'll just state this and then conclude.

There's been some talk about the causes here, and I noticed that, Mr. Neas, in your testimony about why this is happening, you say in your testimony that there are multiple reasons, but insufficient supply of available raw materials is one you cite, inadequate or delayed communications about shortages, and I know the GAO report cites a number of manufacturing-related causes.

I think there's been some indication in Washington here that folks are pointing to price and reimbursement. I think we got a—especially in light of your testimony, how important that was to have you outline what the causes are, not some of the things we've heard from folks here in Washington. That's an important point that you made to help us better understand not just the causes but, therefore, some of the solutions.

I know we're wrapping up, and I'm just grateful that you gave us this time and bring to us your expertise. Thank you.

The CHAIRMAN. Any last thing from any of our witnesses before we adjourn for the day?

[No response.]

If not, I also thank you all very much for your work in this area, your leadership, and for being here today.

I think we got good testimony today from both this panel and the previous panel. It is a complex problem, but I don't think it's unsolvable.

I thank you all very much. The record will remain open for 10 days for Senators to submit any other comments or questions.

And with that, the committee will stand adjourned. Thank you.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF JERRY A COHEN, M.D., PRESIDENT, AMERICAN SOCIETY OF ANESTHESIOLOGISTS; AND ARNOLD J. BERRY, M.D., M.P.H., VICE PRESIDENT FOR SCIENTIFIC AFFAIRS, AMERICAN SOCIETY OF ANESTHESIOLOGISTS

On behalf of the over 48,000 members of the American Society of Anesthesiologists (ASA), we would like to thank Chairman Harkin and Ranking Member Enzi for holding a hearing regarding drug shortages on December 15, 2011, and allowing ASA the opportunity to submit a statement for the record. We greatly appreciate your willingness to bring this important topic before the Senate Committee on Health, Education, Labor, and Pensions and for your efforts to address this issue.

As the recognized leader in patient safety, anesthesiologists are seriously concerned about the toll drug shortages are having on our patients. In April 2011, ASA conducted a survey of 1,373 anesthesiologists to quantify the impact of drug shortages on our patients and practices. Our survey results demonstrated that as a result of drug shortages, 51 percent of anesthesiologists altered a procedure in some way, 48 percent felt shortages resulted in a less optimal patient outcome, 48 percent reported longer operating room or recovery times and 10 percent postponed or cancelled procedures. While these numbers may be alarming they pale in comparison to the 98 percent of anesthesiologists who experienced a drug shortage during the past year, or the 90 percent of anesthesiologists that reported a shortage of 1 or more drugs at the time of the survey.

One of the most common drugs for which anesthesiologists reported a shortage is propofol. In fact, 88 percent of anesthesiologists reported experiencing a shortage of this drug. For anesthesiologists, propofol is one of the most commonly used drugs for the induction of anesthesia or for providing sedation. Other drugs used for these purposes may result in less than optimal patient outcomes including prolonged awakening, longer stays in recovery prior to discharge and increased nausea and vomiting. While anesthesiologists are trained to safely use multiple drugs, and can often find alternatives for drugs in short supply, these shortages can cause decreased patient satisfaction (prolonged awakening, delayed discharge, nausea) or adverse outcomes, including death in extreme situations (e.g., trauma patients, unstable hemodynamics, airway emergencies).

In November 2010, ASA along with the American Society of Clinical Oncology, the American Society of Health-System Pharmacists, the Institute for Safe Medication Practices and the American Hospital Association co-convened a Drug Shortage Workshop Summit.

This Drug Shortage Summit Steering group, consisting of the co-conveners, manufacturers, distributors and group purchasers, released initial findings and continued to meet over the course of the next 10 months producing a series of five recommendations for regulatory and legislative action. The work group made the following recommendations.[1]

1. Reallocate resources within FDA and for the Congress to authorize and appropriate funding for FDA activities that prevent or mitigate shortages.

2. Require manufacturers to report product discontinuations and manufacturing interruptions 6 months in advance or upon determining that production will not meet average historical demand. Establish communications methods to provide accurate and timely information to health care providers. Establish methods to better predict the seriousness and duration of drug shortages.

3. Establish criteria for determining whether a drug is vulnerable to shortage. Designate drugs that are vulnerable to shortage as part of the FDA approval process. Establish appropriate incentives for manufacturing redundancies or other means of producing emergency supplies for drugs that are deemed vulnerable to shortages. The pharmaceutical industry should collaborate with regulatory and legislative entities to identify these incentives.

4. Require collaboration between the FDA Center for Drug Evaluation and Research divisions and the Attorney General to establish a process that would expedite the increase in manufacturing production quotas when needed in response to drug shortages of controlled substances.

5. Leverage current FDA pathways to expedite the approval process for medically necessary unapproved drugs that are vulnerable to shortages without compromising the safety of the drug.

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[1] *Regulatory and Legislative Recommendations from the Drug Shortages Summit Steering Group.* Drug Shortage Legislative-Regulatory Work Group: American Society of Anesthesiologists et al. November 5, 2011. *http://www.ashp.org/drugshortages/summitreport*.

While drug shortages are an issue for patients and physicians, shortages also negatively impact health care costs. Drug shortages have resulted in significant price increases and have often caused providers to search alternative sources to obtain critically necessary drugs. In a recent study, Premier found that the average markup on a drug sold in the grey market is 650 percent. However, for propofol the average markup is a startling 3,161 percent.[2] Anesthetic drug shortages can increase procedure and recovery times as a result of anesthesiologists being forced to select alternative therapies, as well as increase societal and health system costs for cancelled or postponed cases. At a time in which Congress and the Administration are focused on reducing health care expenditures and maximizing patient safety, quality and satisfaction, drug shortages present a considerable obstacle to these important objectives.

Anesthesiologists are end users of drugs and need to be better informed about drug shortages and the duration of the shortages. We are pleased to see that Congress and the Administration recognizes the need for provider notification and has taken steps to address this issue.

Recently, the Administration has taken a number of steps to combat drug shortages. On October 31, 2011, President Obama issued an Executive order that would quicken the review process for applications to start or change production of drugs in shortage, widen the reporting of shortages and expand notifications of shortages and sharing relevant information regarding possible price gouging with the Department of Justice. We commend the Administration for their efforts. These are important steps to address drug shortages, and we fully support them.

Also, we fully support and thank Senator Amy Klobuchar for introducing the bipartisan Preserving Access to Life-Saving Medications Act (S. 296), which would require drug manufacturers to notify the Food and Drug Administration if there is an interruption in manufacturing that could lead to a drug shortage. Currently, the Senate version has 20 cosponsors and continues to gain support. We strongly urge Congress to pass this legislation during the 112th Congress.

In addition, ASA looks forward to working with Senator Hatch as he develops legislation to address drug shortages, and we look forward to working with all members of the Senate Committee on Health, Education, Labor, and Pensions to address this issue.

Again, thank you for holding such an important hearing on an issue that if addressed properly can improve quality of care for our patients.

DEPARTMENT OF HEALTH & HUMAN SERVICES,
FOOD AND DRUG ADMINISTRATION,
SILVER SPRING, MD 20993,
March 27, 2012.

Hon. TOM HARKIN, *Chairman,*
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

DEAR MR. CHAIRMAN: Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the December 15, 2011, hearing before the Committee on Health, Education, Labor, and Pensions entitled "Prescription Drug Shortages: Examining a Public Health Concern and Potential Solutions." We are providing responses for the record to written questions from certain members of the committee sent to us by committee staff on January 19, 2012.

If you have further questions, please let us know.

Sincerely,

JEANNE IRELAND,
Assistant Commissioner for Legislation.

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[2] Cherici, Coleen; Patrick McGinnis and Wayne Russell. *Buyer Beware: Drug Shortages and the Gray Market.* Premier Inc. August 2011. *http://www.premierinc.com/about/news/11-aug/Gray-Market/GrayMarket-Analysis-08152011.pdf.*

RESPONSE TO QUESTIONS OF SENATORS CASEY, BLUMENTHAL, ENZI, BURR, AND HATCH BY THE FOOD AND DRUG ADMINISTRATION

QUESTIONS OF SENATOR CASEY

Question 1. Some people have suggested that drug shortages are, at least in part, related to changes in regulatory actions and standards, as well as increased enforcement, on the part of the FDA. For example, some have suggested that the FDA is now requiring manufacturers, in particular sterile injectable manufacturers, to meet higher levels of quality for processes and products than it did over the past few decades. Can you comment on whether the FDA Good Manufacturing Practices (GMPs) or other standards have changed with respect to sterile injectables? Have the amount of resources, or the priority that FDA has placed, for enforcement of GMPs and other standards increased in the past few years for sterile injectables? Finally, can you comment on whether technology has changed over the past decade in a manner that allows the FDA and/or manufacturers to track the purity of drugs, or the quality of drug products and manufacturing processes, in a way that was not previously possible?

Answer 1. The trend of increased drug shortages does not correspond to an increase in regulatory requirements. FDA does everything in its power to prevent and/or mitigate drug shortages, including exercising regulatory flexibility. FDA carefully considers the impact of any drug shortage on patient care and access before taking any enforcement action.

There have been no recent major changes to the Current Good Manufacturing Practice (CGMP) regulations that would substantially impact drug product manufacturing, including sterile injectables. The CGMP regulations for finished pharmaceuticals are the minimum standard by which drugs must be manufactured, and are written to be flexible and adaptable to newer manufacturing technologies and analytical techniques. The CGMP regulations ensure that consumers have drugs made with the correct ingredients, have been processed in a controlled manner to ensure delivery of the safe and effective amount of the active ingredient, are free of harmful contamination, and will remain safe and effective throughout the labeled shelf life.

In September 2008, FDA finalized minor changes to its CGMP regulations for aseptic processing to incorporate a long-standing, enforced Agency interpretation, and there were no significant objections to this revision. FDA's "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice," was last revised in 2004 using a public notice and comment process and was well accepted by manufacturers at the time of finalization. Note that FDA guidance documents represent the Agency's current thinking on a topic. Guidance documents are not mandatory and do not operate to bind FDA or the public; alternative approaches may be used if the approach satisfies the requirements of the applicable statutes and regulations. We are unaware of any changes to private or other standard-setting organizations, including the United States Pharmacopeia, in a way that imposes a higher-quality level on sterile injectable drugs.

Sterile injectable drug manufacturing operations are vulnerable to microbiological contamination and require more complicated controls and equipment. For many years, due to heightened patient safety concerns, FDA has made such drugs a higher-inspection priority, but there have been no recent changes to the FDA inspection program for sterile injectable manufacturing operations.

FDA has exercised substantial regulatory flexibility in working with firms experiencing CGMP problems to help them identify and resolve quality problems and get their drugs back to market as expeditiously as possible. Sterile injectable drugs have unique manufacturing and market features, which make shortages of these products more likely to occur and harder to prevent or mitigate. These include:

- Manufacturing operations are complicated to control and more vulnerable to problems that affect safety (e.g., microbiological contamination);
- Dedicated manufacturing lines are often required;
- The top three generic injectable manufacturers hold 71 percent of the market for generics, by volume;
- Most sterile injectables have one manufacturer that produces at least 90 percent of the drug (innovator and generic combined); and
- "Just-in-time" manufacturing and inventory practices leave little margin for error.

Technology has improved over the past decade in the area of sterile drug product processing and test methods, but not all advances have been widely adopted. Methods to measure air quality and microbiological contamination in the manufacturing environment now permit more consistent and rapid detection of these types of hazardous contamination. Automated methods to detect and quantify foreign particles

in sterile injectable liquids have also improved over the past decade, although such methods are not in common use and are not required by FDA. The quality standards in such areas allow for minor variations, so improvements in detecting such contamination would not necessarily result in a greater number of batch failures or disruption to manufacturing capacity.

The past two decades have also seen improvements in preventing objectionable contamination in sterile injectables. Processing methods increasingly incorporate equipment and techniques designed to reduce contamination—microbiological and other—in sterile injectables. Many of the processing advances decrease the amount of operator access—a primary source of microbiological contamination—to the critical processing areas where vials are open to the environment. FDA has encouraged manufacturers of sterile injectables to adopt processing methods that improve sterility assurance. Together, these advances represent important steps forward in improving the quality of manufactured products.

Question 2. In your testimony you note that of the 127 drugs in shortage that the FDA tracked during 2010–11, 43 percent were innovator drugs. I assume that by innovator drugs, you mean brand name drugs (i.e., drugs that are still under patent). I thought that it was interesting that more than two in five drugs in shortage were innovator drugs given that we have heard some people say that low reimbursement is one of the causes of drug shortages. But if a drug is still on patent, its manufacturer can really charge whatever price it needs. Does that imply that the causes of drug shortages are more complicated than just pricing or reimbursement, and if so, to what causes do you attribute the shortages among innovator drugs?

Answer 2. Yes, the causes of drug shortages are more complicated than pricing or reimbursement. The main causes of drug shortages for the past 2 years are similar for both innovator (brand name) drugs and generic drugs and have included:

- Problems at the manufacturing facility (43 percent of drugs in shortage tracked from January 2010–August 2011);
- Delays in manufacturing or shipping (15 percent of drugs in shortage tracked from January 2010–August 2011); and
- Active pharmaceutical ingredient shortages (10 percent of drugs in shortage tracked from January 2010–August 2011).

In our experience, the factors that contribute to drug shortages, both innovator and generic drugs, generally include:

- Industry consolidation and limited capacity (many innovator products are made by contract manufacturers that make multiple drugs on the same manufacturing lines and the capacity is often limited);
- Difficulty in producing a given drug;
- Quality and manufacturing problems (in some cases facilities have not been upgraded appropriately, equipment has not been maintained properly, and appropriate quality systems are not in place);
- Unanticipated increases in demand;
- Inventory and distribution practices (which may lead to regional shortages); and
- A business decision to discontinue manufacturing the product (e.g., in favor of producing a more profitable drug or because the product is not profitable).

Discontinuances caused 8 percent of shortages in 2010 and 2011 and have usually involved older sterile injectables that were discontinued for business reasons, such as to make production room for a different, more profitable product. Economic factors may also influence a firm's decision to not maintain their facilities and quality systems adequately. For example, manufacturers may continually decrease idle time for their manufacturing lines, running them in production mode continuously. This practice puts stresses on the production equipment and makes little time available for maintenance and repairs.

Question 3. In your testimony you note that in 4 weeks following the issuance of the President's Executive order, you received a sixfold increase in notifications from manufacturers. Can you comment on whether the types of things that you were notified about were materially different from previous notifications? Are you now hearing from a broader group of manufacturers?

Answer 3. Yes, we are hearing from a broader group of manufacturers. However, the types of issues that manufacturers notify FDA about have not substantially changed and include the following:

- Quality defects or other problems they are experiencing that are causing actual or potential shortages;
- Requests for expedited review of changes in manufacturing, new manufacturing sites, new suppliers, or other changes;

• Delays or temporary unavailability for any reason;
• Potential shortages for any reason, with requests that the normal importation process be expedited for their approved raw materials or approved finished goods.

Question 4. In your testimony you note that the FDA is assessing commercial systems that could be contracted to provide ongoing or periodic data on sales and distribution of drugs at the wholesale level to detect early signals of potential shortages or supply disruptions. Can you comment on the FDA's current ability to—at a bird's eye view—identify and track shortages? Can you further describe efforts underway to identify such a commercial system and what types of conversations you are having with manufacturers and distributors about such an initiative? Do you have an estimate of what types of resources would be required to execute such contracts?

Answer 4. FDA's Drug Shortage Program is currently able to track and monitor shortages and potential shortages that are reported to us. What we are trying to ascertain is whether there are ways we might track and monitor factors that could predict products or facilities that are at high risk for leading to drug shortages. To date, we have not identified any commercial sources for these types of data. We are also aware of academic centers working on development of such data, but their efforts have not yet yielded useful information, either. Therefore, we have begun to examine our own sources of data, such as records of facility inspections and other compliance activities, to determine whether any factors alone or in combination are predictive enough to serve as a bellwether. This process is extremely labor-intensive and data must be compiled manually.

Data from wholesalers and distributors may provide signals that a shortage is already underway; however, we prefer to have notification of shortages or potential disruptions in supply from the manufacturers themselves so that we can offer assistance, before the shortage reaches the wholesalers and distributors. Therefore, FDA has continued to encourage manufacturers to notify the Agency of any shortage or potential disruption in supply. In addition, on December 19, 2011, FDA issued an Interim Final Rule (effective January 18, 2012) that expanded the circumstances required to be reported to FDA related to "discontinuances."

In February 2012, FDA issued a Draft Guidance, explaining the amendments to the implementing regulations published as an interim final rule on December 19, 2011 (effective January 18, 2012). It provides guidance to industry on voluntary notification to FDA of issues that may result in a shortage or potential disruption in supply of a prescription drug or biological product in the U.S. market, regardless of whether mandatory notification is required under section 506C.

Question 5. In your recommendations you note that the FDA has doubled the number of staff to help alleviate drug shortages. Since the Drug Shortage Program is currently housed within the Center for Drug Evaluation (CDER), can you comment on how this work is funded? Is any funding drawn from user fees?

Answer 5. The additional staff are predominantly on temporary assignment from their positions in a number of offices from across CDER. This allows us to assess how best to plan for hiring of permanent positions, while we address current shortage prevention and mitigation. These staff positions are funded in part by user fees and in part by appropriated funds.

Question 6. Can you comment on the broader resource needs at the FDA (e.g., technological, infrastructure, or otherwise) for appropriately preventing, identifying and tracking, and managing and resolving drug shortages? Would it be preferable to establish a separate Center for Drug Shortages and directly fund that entity so that it can appropriately staff itself and make much-needed investments in technology for tracking drug shortages, as identified in the recent GAO report?

Answer 6. The Drug Shortage Program (DSP) has grown from 3 full-time staff members in 2010 to 11 full-time staff members in February 2012. DSP coordinates tracking and responses to prevent and address shortages. DSP creates a team of experts throughout the Agency for each shortage issue. The specific disciplines involved in each shortage team vary, depending on the issues involved and can involve physicians, chemists, microbiologists, manufacturing and compliance experts, and many others. It is important to note that not all shortages can be prevented or resolved quickly due to the significant safety and quality issues that may be involved. However, in all cases, FDA utilizes a team of experts and employs all available tools to prevent and address the shortage or disruption in supply.

Relocation of the DSP outside of CDER would not improve tracking or the Agency's response to drug shortages. DSP's presence within CDER greatly facilitates its ability to effect collaboration in addressing and preventing shortages. There is a

large pool of experts within CDER, called upon to assist with drug shortages, and DSP engages other offices outside of CDER when necessary.

Question 7. Can you comment on specifically how the Drug Shortage Program (DSP) works with others within the FDA, including the Office of Commissioner, to ensure that drug shortages are prevented as much as possible, and resolved as quickly as possible? What sort of coordination and communication occurs between DSP and different relevant centers at the FDA, and how regularly does it occur? What barriers stand in the way of achieving better coordination and communication within the FDA? As Mr. Neas shared in his testimony, the generic pharmaceutical industry strongly encourages the establishment of a high-level FDA drug shortage management team, which would include representation from key agency offices. What do you think about this proposal?

Answer 7. FDA is committed to prevent and address drug shortages. CDER works diligently to coordinate across all offices to resolve drug shortages expeditiously. DSP works closely with CDER's Office of Compliance (CDER/OC), Office of Generic Drugs (OGD), and Office of New Drug Quality Assessment in an effort to prevent or mitigate drug shortages. Communications between various offices within CDER regarding shortages occurs daily. This includes communications between DSP, CDER/OC, and the review divisions. That said, we know we can always improve and we have a Drug Shortage Network in place with key individuals assigned to work on shortage issues in each of these offices so that timely communications occur within CDER and between CDER and other offices and Centers as needed, regarding shortages. CDER also engages FDA's Office of Regulatory Affairs (ORA) to coordinate domestic and international investigations and inspections as necessary. The Office of the Commissioner is also involved to provide policy guidance and analytic assistance as needed by CDER.

Communications between Centers regarding shortages occurs when a shortage issue affects more than one Center. This occurs rarely and could involve, for example, a manufacturer experiencing quality issues that involve veterinary drugs, human drugs, and vaccines. This example would involve three Centers in FDA, and the shortage programs in all three Centers would work together to coordinate all actions and responses to the shortage. The shortage programs in the different Centers have shared best practices and continue to do so.

FDA continues to improve coordination and communication, both within CDER and with other parts of the Agency. For example, FDA formed an additional working group to concentrate efforts on improved communications and coordination by and between ORA district offices and CDER. Additionally, we have identified dedicated Drug Shortage Coordinators in each ORA District Office. These coordinators will facilitate communications with the Center, which, in turn, increases the number of early notifications to CDER that firms are planning to cease or slow production or are experiencing significant quality problems that could lead to a shortage.

A high-level drug shortage management team is thus already in place and includes the Drug Shortage coordination staff as well as a high-level team of experts from across FDA who possess the specific knowledge and skills needed to help address and prevent shortages. The current structure allows us the flexibility to adapt to changing circumstances, while still ensuring communication and coordination.

Question 8. Can you comment on how well the FDA has been able to develop and institutionalize a comprehensive and cross-center strategic plan to address drug shortages that will hopefully, over time, help to reduce the number of shortages?

Answer 8. DSP has an established network of experts involved in shortage management and prevention. This team includes individuals from across the Center and involves compliance/manufacturing experts, chemists, microbiologists, toxicologists, and clinicians who are called upon to assist with addressing and preventing shortages. FDA has established a Drug Shortage working group to continue to investigate the causes and solutions to shortages and to improve communications between the various components of the Center as well as between the field offices and the Center.

QUESTIONS OF SENATOR BLUMENTHAL

Question 1. Dr. Kweder, what type of data is FDA keeping about these shortages and their efforts to mitigate such shortages? Why are these shortages lasting for, on average, 9 months? What actions are taking place during those 9 months to mitigate the shortage?

Answer 1. FDA developed a database to track the numbers of shortages, the types of products in shortage, the reasons for the shortages, and the FDA actions taken to help resolve and prevent the shortages. FDA re-assesses all shortages and poten-

tial shortages daily and is doing all that we can within our authority to prevent and address shortages.

Some shortage problems, such as loss of a manufacturing site or severe manufacturing or quality problems that could pose a considerable risk to patient safety, may take firms significant time to resolve. If there are no other manufacturers able to increase production of the product quickly (usually due to capacity limitations) or available product for import, then more time may be required while the original manufacturer works to address the quality problem and bring the product back online. However, if there are ways that FDA is able to help, such as assisting with a quality problem when there is not a significant risk for patients, or expediting review of changes in manufacturing sites, suppliers or processes, these issues can be addressed quickly, sometimes in days or weeks. An example of this is a potassium phosphate injection that had particulate matter in the vials. The firm was able to show with data submitted to FDA that the particulate matter could be successfully removed by a filter and the drug was able to be shipped with the filter and instructions for pharmacists to use the filter with the drug to prevent risks for patients. The review of this issue was completed within days after receiving the proposal from the firm.

In cases where a long-term shortage is anticipated, FDA searches for firms that manufacture drugs for foreign markets and would be willing and able to temporarily import a drug that could help meet critical patient needs. Temporary importations have occurred for nine drugs over the past 2 years. Five of those drugs are currently being temporarily imported. FDA evaluates the drug available in the foreign market to ensure there are no significant safety problems for U.S. patients and that it is made in a manufacturing site that meets FDA standards. FDA is not always able to find a firm willing and able to import to address a shortage; however, it is something that we explore when there is a long-term shortage of a critically needed drug.

Question 2. Dr. Kweder, what is the relationship between shortages in the United States and abroad? Are the same shortages felt internationally, generally? Or is the United States in a unique position?

Answer 2. FDA is working closely with other regulatory authorities in Europe, Australia, the United Kingdom, and Canada on existing drug shortage problems, as drug shortages are not unique to the United States, but are a global problem. For example the recent Doxil shortage has affected Europe, Canada and the United States. During our discussions with international regulatory agencies, crucial information regarding the availability of important drug products and potential alternate facilities is shared. Additionally, when quality problems, manufacturing constraints, or limited production capacity trigger a shortage, FDA and other regulatory authorities exchange information regarding the issues identified or leading to the drug shortage. These regulatory authorities then communicate, when necessary, with industry to explore options that will best address patient needs.

QUESTIONS OF SENATOR ENZI

Question 1. What is the average and range for how long it takes to get FDA approval for a manufacturing facility change? Please provide specific examples where FDA met the 6-month goal.

Answer 1. The 6-month goal you reference relates to applications for manufacturing facility changes that require prior approval. Under the Prescription Drug User Fee Act (PDUFA), FDA committed to reviewing 90 percent of such supplements within 6 months. In fiscal year 2011, FDA reviewed 98 percent of these supplements in 6 months, exceeding the goal agreed to with industry.

FDA does not track the specific data you requested; however, the time it takes for approval of a manufacturing facility change will depend on several factors:

- whether the new site has ever been inspected;
- whether the new site has any quality problems that have been identified;
- location of the site, since an overseas inspection may take longer to schedule due to current resource constraints;
- whether the site makes similar drugs for the U.S. market;
- whether the application for the change contains all of the information needed to review the change (sometimes applications are missing essential data).

Depending on the type of facility change, sometimes these changes can be submitted as "change being effected (CBE)-30 supplements," which means that 30 days after the submission, the firm can release the new production from the new site unless FDA objects. A recent example is a firm that needed a new site to increase supplies of a cancer drug and two other drugs in shortage. We accepted the site addi-

tion as a CBE–30 supplement because the firm was recently inspected, had no quality concerns, and makes similar drugs for the U.S. market.

For drugs in shortage or for those with potential for shortage, FDA works closely with the firms so that their applications and inspections can be expedited.

Question 2. What percentage of manufacturing changes requires prior approval by the FDA, and how does that compare with the EU?

Answer 2. FDA does not compare and/or tally the different types of manufacturing changes in this manner. However, while not an exact match, the requirements for filing manufacturing changes in the European Union (EU) are similar to the FDA. Not all changes require prior FDA approval (for example, the CBE–30 supplements discussed above) and for those that do, any shortage related applications—requiring prior approval or not—are expedited.

Question 3. Please identify the specific drug shortages you have prevented and describe how you did it. How do you define a prevented shortage?

Answer 3. FDA regularly intervenes in potential shortage situations to help prevent or minimize shortages. Since October 31, 2011, when the President issued his Executive order, FDA has worked closely with manufacturers to prevent 114 drug shortages.

- Of the drugs involved, 86 were manufactured by one firm. The firm had lost the supplier that it used for material in the container for these products. FDA worked closely with the firm to quickly qualify and approve the new supplier and was able to prevent shortages of the affected drugs.
- The other 28 potential shortages involved different causes and solutions:
  - Expedited Importation (two potential shortages): Impending shortages of two drugs were averted by expediting the importation of these approved drugs from outside the United States. Both of these approved drugs are manufactured overseas for the U.S. market. The U.S. inventory levels of these drugs were insufficient to meet demand. With respect to one of those drugs, there was an unanticipated increase in demand and the manufacturer needed FDA's assistance to respond to that demand. In the second case, a manufacturing delay caused a reduction in supply. In both cases, FDA expedited the importation process so that the drugs could be imported quickly to avoid a shortage.
  - Quality Problems (14 potential shortages): During the same time period, FDA prevented 14 of these potential shortages by rapidly addressing quality problems.
  - One potential shortage involved a firm that had a slightly out-of-specification test result for their finished drug product, but which did not represent significant risk for patients. Therefore, FDA allowed the firm to ship the finished product in inventory, while they corrected the problem for future lots.
  - The second potential shortage resulted from a quality issue with the glass used for syringes for use with a particular drug. With guidance from the Agency, the firm was able to do additional testing to remove all of the defective syringes from the batch, before releasing the product to the market.
  - The third potential shortage involved a quality problem at the manufacturing site of a manufacturer that makes sterile water used to dilute injectable drugs that are in a powder formulation and that need to be reconstituted before use. FDA determined that the quality issues did not have an impact on the sterile water vials, so we permitted the firm to release the drug with the sterile water vials while it worked to correct the problems at the manufacturing facility.
  - The fourth potential shortage involved glass particles in vials of a medically necessary drug. Working with the Agency, the firm was able to show that pharmacists could successfully filter the drug to remove the glass if they were provided with adequate instructions, and that there would not be a significant risk to patients from the filtered drug. FDA, therefore, permitted the firm to release the drug with approved instructions to filter the drug before use.
  - The remaining issues involved general systems problems at manufacturing sites that could have had an impact on the safety or quality of the drugs made in the facilities. FDA worked closely with the firms, and they were able to take additional steps to ensure that there were no significant risks for patients due to the issues and that the drugs could be released to avoid a shortage while the firms corrected the problems.
  - Expedited Review of Supplements (nine potential shortages): These involved firms that needed new facilities, new suppliers, and/or changes to their product formulation approved to avoid shortages. For example, one firm shut

down its original manufacturing site and opened a new facility. As required by law, the firm submitted a "supplement" to its application to seek FDA approval to manufacture the drug product at the new facility. FDA expedited the inspection of the facility and approval of the supplement, completing review, inspection, and approval in 60 days—well in advance of the PDUFA goal of 6 months—to avoid a shortage of the product.

- Increased Production (three potential shortages): With respect to the remaining three potential shortage situations, FDA worked with alternative manufacturers of drugs that were facing potential shortages to ramp up production to cover the anticipated shortfall. In these situations, FDA learned that the manufacturer in question was facing problems (two involved quality problems and one involved a product recall). As soon as FDA became aware of potential shortages of the products in question, we initiated an outreach program and worked with other manufacturers to avert the shortage.

Question 4. How many more notifications do you expect with the change in the IFR, and how do you define an action that may precipitate a shortage?

Answer 4. The Interim Final Rule (IFR) defined the term "discontinuance" in FDA's regulations to include both temporary and permanent interruptions in the manufacturing of a drug product, if the interruption could lead to a disruption in the supply of a product. The IFR also clarified the definition of the term "sole manufacturer" to refer to an applicant that is the only entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States, whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities.

We anticipate an increase in notifications as a result of the IFR. It is difficult to predict how many additional notifications will occur with the change in the IFR; however, FDA is continuing to see an increased number of notifications in 2012 from manufacturers, some of which are a direct result of the IFR. The earlier FDA learns of a drug shortage, the more effective FDA can be in helping to minimize the impact on patients and health care professionals. For this reason, legislation requiring early notification of impending supply disruptions and discontinuation of drugs is a necessary tool in mitigating or preventing shortages.

QUESTION OF SENATOR BURR

Question. How many of the drugs recognized to be in shortage by the FDA are drugs for which generic drug applications are currently pending review by FDA? How many of these generic drug applications for drugs currently experiencing a shortage, or that have experienced a shortage over the past 5 years, have been pending review past the 6-month statutory review timeframe?

Answer. We are not aware of any such applications. FDA's OGD routinely monitors the queue of generic drug applications and takes action when an application involves a product that may help prevent a shortage or resolve one. With respect to new applications, OGD regularly monitors all incoming applications to determine whether any are for drugs that are facing a shortage situation. When we identify an application relating to a drug in shortage, we designate the application for expedited review and proceed with the review on that basis. Notwithstanding expediting the review of applications for generic products that may help alleviate a drug shortage, all applications still must meet FDA's standard for approval.

There are reasons why a generic application associated with a shortage drug could and would remain "pending" after a successful review and inspection. In some cases, an application cannot be granted final approval because the brand in shortage holds a valid patent that the generic-application sponsor has chosen not to challenge. In that case, FDA cannot approve the generic application until the patent expires. Another issue that could affect the review time of a drug in shortage is that it is not always possible to know ahead of time that a product will be in short supply. As mentioned above, new applications relating to drugs in shortage are designated for expedited review, but it is possible that, prior to a particular drug going into shortage, an already existing application would be pending with FDA and appropriately proceeding through the queue. This may be why applications appear to be pending for some period of time for drugs on the shortage list, especially if the drug was recently added to the shortage list.

QUESTIONS OF SENATOR HATCH

Question 1. How does the Office of Drug Shortage work with the Office of Compliance? Do they consult one another before taking action to relieve or mitigate short-

ages? Do they consult one another before taking enforcement actions that could lead to shortages?

Answer 1. Staff in DSP and CDER/OC communicate almost on a daily basis to discuss potential and actual shortages. The Office of Drug Security, Integrity, and Recalls (ODSIR), Recalls Coordinating Branch (RCB) within CDER/OC, is the liaison to DSP. CDER/OC reports weekly to DSP a summary of all pending CGMP regulatory cases.

DSP is notified prior to a CGMP enforcement action, such as a Warning Letter, seizure, and injunction, to help evaluate and/or mitigate the impact such actions may have on medically necessary products. In addition, if severe violations are identified during an inspection, the investigators contact CDER/OC, who in turn, will notify DSP of the violations and have a market impact evaluation done, unless it is obvious that the products affected are not medically necessary. The potential for shortage is evaluated along with the impact the shortage would have on patients, as well as any risks involved with the drugs in question. Decisions about specific regulatory compliance actions take into account their potential impact on availability of drugs, the medical necessity of those drugs in clinical practice, and the level of risk involved with a firm's manufacturing and CGMP deficiencies. In all cases, FDA works closely with the firm(s) to minimize any risks while working to restore and maintain safe supplies.

Question 2. How many of the products in shortage were provided with a warning letter from the Office of Compliance prior to being in shortage? Of those products, how many warning letters were specifically regarding the safety of the product sold on the market?

Answer 2. This information is not readily available, although we do know that 43 percent of shortages are related to problems at the manufacturing facility. We are conducting a comprehensive, retrospective review to see if manufacturers of products in shortage received a Warning Letter prior to the shortage. This is resource- and time-intensive. We will share the outcome of our review once it is available.

Question 3. Is it accurate to say that FDA inspects Contract Manufacturing Organizations when the organization enters into a new contract with an innovator to manufacture a particular product? If so, would it not be better to provide a general quality system review when requested by the CMO as opposed to waiting for the organization to enter into a contract? It is my understanding that manufacturers prefer contracting with CMOs that are already FDA-approved, many of which are abroad. If the CMO is pre-approved prior to the contract, could that not help to alleviate shortages by increasing U.S. manufacturing capacity?

Answer 3. FDA inspections of manufacturing sites are prompted by the site's registration with FDA, which is required when a site begins to manufacture and distribute drugs and when a site is identified in a new drug application. For drug manufacturing sites that are listed with FDA, we perform routine inspections and, where appropriate, we will use information from a routine inspection to waive a pre-approval inspection before additional drugs are made at the facility. In other words, we already consider a listed site's compliance with CGMPs—and each CGMP inspection must cover the site's quality system—in deciding whether to approve a manufacturing site for additional application drug products. If we were to inspect before the time a contract is signed, this could result in unnecessary site inspections, for example, if a site is not, in fact, named in an application.

Question 4. Do you believe the proposal offered by the Generic Pharmaceutical Association will have a significant impact on drug shortages? Do you believe the FDA is already filling the role of the third party entity they suggest establishing for purposes of coordination? If not, how is it different?

Answer 4. FDA has met with Generic Pharmaceutical Association and will continue to work with them on shortages. We recently heard some initial information from them about their proposal, the Accelerated Recovery Initiative. There is not yet enough information provided to FDA to make a determination about the impact this proposal could have on drug shortages.

[Whereupon, at 12:44 p.m., the hearing was adjourned.]

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