S. HRG. 112–667

DRUG SHORTAGES: WHY THEY HAPPEN AND WHAT THEY MEAN

HEARING

BEFORE THE

COMMITTEE ON FINANCE
UNITED STATES SENATE

ONE HUNDRED TWELFTH CONGRESS

FIRST SESSION

DECEMBER 7, 2011

Printed for the use of the Committee on Finance

U.S. GOVERNMENT PRINTING OFFICE

77–601—PDF WASHINGTON : 2011

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
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DRUG SHORTAGES: WHY THEY HAPPEN AND WHAT THEY MEAN

WEDNESDAY, DECEMBER 7, 2011

U.S. SENATE,
COMMITTEE ON FINANCE,
Washington, DC.

The hearing was convened, pursuant to notice, at 10:05 a.m., in room SD–215, Dirksen Senate Office Building, Hon. Max Baucus (chairman of the committee) presiding.

Present: Senators Bingaman, Wyden, Carper, Cardin, Hatch, Grassley, Cornyn, and Thune.

Also present: Democratic Staff: Russ Sullivan, Staff Director; David Schwartz, Chief Health Counsel; Matt Kazan, Professional Staff; and Callan Smith, Research Assistant. Republican Staff: Chris Campbell, Staff Director; and Daniel Todd, Health Policy Advisor.

OPENING STATEMENT OF HON. MAX BAUCUS, A U.S. SENATOR FROM MONTANA, CHAIRMAN, COMMITTEE ON FINANCE

The CHAIRMAN. The hearing will come to order.

The American inventor Charles Kettering once said, "A problem well stated is a problem half solved." We are here this morning to make sure we state the problem of drug shortages well, because doing so will help us find a solution.

In a recent study, nearly every hospital surveyed had experienced at least one drug shortage in the past 6 months, and nearly half of the hospitals experienced 21 or more shortages during that same period. These shortages affect some of the sickest and most vulnerable Americans.

As Dawn Grayson from Billings, MT can tell you, when someone you love cannot get the medicine they need, it can be terrifying. This April, Dawn gave birth to a beautiful baby boy named Tanner. Tanner was born 11 weeks premature. He developed a serious, and sometimes fatal, infection and had to have emergency surgery. Because of his condition, Tanner could not take a bottle like other babies. Instead, he had to get all his nutrients, including calcium, through an IV mixture.

But there is a national shortage of the type of calcium that Tanner needed. Calcium is critical for muscle function and bone-building, especially in young children, and he could not go without it. So, as is too often the case with shortages, the hospital had to give Tanner a substitute, and that substitute caused complications.

In Tanner's case, the substitute caused chemical burns and premature scarring on his arm and his foot. Dawn is concerned it will

affect Tanner's mobility as he gets older. Dawn said, "My son has enough problems being premature without adding chemical burns on top of an already-difficult condition." She hopes that sharing her story will help us save other families who are going through the same pain.

The number of patients like Tanner who are affected by drug shortages has grown over the past several years. More than half a million cancer patients were affected by drug shortages last year. We have a responsibility to ensure that Medicare and Medicaid beneficiaries, and all Americans, have access to the care they need. We need to fix this problem to make sure this does not happen to more patients like Tanner.

Drug shortages deserve more attention, so I am glad Senator Hatch and I were able to schedule this hearing. We are pleased to see that this issue is also receiving greater attention. Specifically, Senator Hatch, Senator Tester, and Senator Klobuchar have worked hard on it, and I commend them.

Drug shortages are not a new problem, but the number of drugs and patients affected over the past several years has grown at an alarming rate. There were shortages on 211 drugs last year. That is up from 58 shortages in 2004.

The types of patients affected by shortages show how serious this is. We read heartbreaking stories of drug shortages forcing cancer patients to forego critical treatment. We hear stories about emergency room providers forced to use makeshift drugs when conventional drugs are in short supply.

Each drug shortage has its own story. The causes vary. They include quality control issues, delays in manufacturing, disruptions of the supply of raw materials, and changes in the prices of drugs. The variety of reasons that cause drug shortages make it difficult to find one silver-bullet solution, but we cannot tackle this problem without fully understanding the root causes.

Medicare and Medicaid pay for over $26 billion in prescription drugs each year. Both programs have a significant impact on the drug market. I look forward to hearing from our panelists where Medicare and Medicaid fit into this problem, and I look forward to hearing how these programs can be part of the solution. Are there things that we can change? Are there things we can do? What can we do? Will there be unintended consequences to some of these changes?

So, as Mr. Kettering advised, let us work together today to state the problem well; then let us find the solution. Let us help prevent cases like Tanner's from happening to others. Let us help patients like Tanner get the care they need, and let us help moms like Dawn get the certainty they deserve.

[The prepared statement of Chairman Baucus appears in the appendix.]

The CHAIRMAN. Senator Hatch, I am sure, is on his way, so I will now introduce the witnesses.

Today we hear from Dr. Kasey Thompson, vice president of the American Society of Health-System Pharmacists. Welcome, Dr. Thompson.

Next is Dr. Patrick Cobb, an oncologist and hematologist at the Frontier Cancer Center in Billings, MT. Welcome, Dr. Cobb.

Dr. Scott Gottlieb is a resident fellow at the American Enterprise Institute for Public Policy Research. Welcome, Dr. Gottlieb.

And Dr. Rena Conti is assistant professor of health policy and economics at the University of Chicago. Welcome, Dr. Conti.

I would remind all of you your prepared statements will be in the record for everybody to read. In the meantime, I would like you to summarize your statements clearly, succinctly. Do not hold back, and tell us what is on your mind.

Dr. Thompson, you are first.

STATEMENT OF DR. KASEY THOMPSON, VICE PRESIDENT, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, BETHESDA, MD

Dr. THOMPSON. Good morning. Thank you, Chairman Baucus and distinguished members of the committee, for holding this hearing. My name is Kasey Thompson, and I am vice president of policy, planning, and communications for the American Society of Health-System Pharmacists.

I am here today to talk about the problem of drug shortages and how shortages are affecting patients and the ability of health care providers to care for them. For the last 10 years, ASHP, in collaboration with the University of Utah Drug Information Program, has been tracking drug shortages and making that information available to the public on our website.

In the past 5 years, shortages have rapidly escalated, increasing from 70 in 2006 to 231 as of this November, and there appears to be no end in sight. Generic injectable drugs, which are commonly used in hospitals, comprise the majority of drug shortages.

Many drugs fundamental and essential to care are in scarce supply, including oncology drugs, anesthetics, pain medications, antibiotics, and life support drugs for emergency care and intravenous nutrition. Because shortages affect our hospitalized and most vulnerable patients, patient safety and quality are our primary concerns.

Without access to the preferred drug treatment, clinicians must use alternatives which may be less effective or associated with increased risk of adverse outcomes. Examples of these events are described in detail in the Institute for Safe Medication Practices Survey from September 2011.

In this survey, 1,800 respondents reported over 1,000 adverse drug events caused by shortages. Twenty-five percent of these reports were medication errors; another 20 percent were adverse drug reactions. A survey conducted by the American Hospital Association in July 2011 also identified suboptimal care, indicating that 82 percent of hospitals reported delayed treatment, and more than half said they could not provide some patients with the recommended therapy.

Drug shortages also add to the cost of providing care. A study by Premier in March of this year estimated the cost of purchasing alternative therapeutic products for those in shortage to be $200 million annually. In addition, a survey conducted by ASHP and the University of Michigan indicated that hospital pharmacists are spending 8 to 12 additional hours per week dealing with shortages.

Further, the study estimated additional annual labor costs to hospitals in managing shortages to be $216 million annually. Every minute spent dealing with a shortage is time taken away from patient care. In some cases, we were able to determine why there is a shortage; in other cases, we simply have no idea.

As a first step, we support the passage of the current bipartisan legislation in the House and Senate that would help the FDA prevent some shortages from occurring if they were notified about a manufacturing problem or planned discontinuation.

FDA data indicate that 54 percent of drug shortages are related to product quality problems, followed by a lack of capacity or other manufacturing issues. About half of the time manufacturers do not disclose the reason for a shortage.

Our analysis over the last 10 years has shown that many drug shortages are the result of quality issues in the manufacturing process; loss of a manufacturing site; delays and capacity issues; shortages of raw materials, particularly a single source of an active pharmaceutical ingredient; product discontinuations; and secondary shortages of therapeutic alternatives resulting from a primary shortage.

We recognize that there is no one cause of drug shortages and, therefore, there is no one solution. We are very pleased to see other facets of drug shortages, including economic factors, being considered, but we are not currently in a position to draw any conclusions given a lack of sound data.

A recent report by the Assistant Secretary for Planning and Evaluation described the economic analysis of drug shortages. It identified a number of possible factors influencing drug shortages and noted that shortages have been concentrated in drugs where the volume of sales and drug prices were declining in the years preceding a shortage, suggesting that manufacturers are diverting capacity from shrinking lines of business to growing ones.

It has been suggested that Medicare reimbursement policies may be partially to blame for drug shortages. While we believe this is an area that should be explored further, we are hesitant to focus on any one potential cause given the limited data and numerous factors that contribute to shortages. It will be important to learn from other stakeholders in the supply chain, including pharmaceutical manufacturers, wholesalers, group purchasing organizations, and others in order to fully assess these causes and offer solutions to this public health crisis.

Other incentives for manufacturers to stay or reenter the market should be examined. For example, tax credits awarded to companies for developing new technologies in the production process should be explored. We believe that any incentive should be geared toward increasing production capacity and upgrading facilities in order to meet demand for critically important generic injectables.

In conclusion, drug shortages continue to be a very serious public health crisis and compromise our ability to treat adult and pediatric cancer, to feed newborns intravenously who cannot eat, to relieve pain, to battle serious infections, and to provide care when the most appropriate drug is unavailable.

We look forward to working with Congress, the FDA, and other stakeholders to ensure an adequate supply of critical, life-saving

medications. Again, thank you, Mr. Chairman, Ranking Member Hatch, and all members of the committee, for the opportunity to provide input on this urgent public health crisis.

The CHAIRMAN. Thank you very much, Dr. Thompson.

[The prepared statement of Dr. Thompson appears in the appendix.]

The CHAIRMAN. Senator Hatch has arrived, and I would very much now like to turn to him for any statement he may wish to give.

OPENING STATEMENT OF HON. ORRIN G. HATCH, A U.S. SENATOR FROM UTAH

Senator HATCH. Thank you, Mr. Chairman. Sorry I was a little bit late this morning. Mr. Chairman, I want to thank you for convening today's hearing on such an important issue affecting our Nation's patients and caregivers.

We have all seen the disturbing stories in the press over the past several months about doctors unable to access critical medical products for their patients and the impact that these drug shortages have had on patient care. While there is no doubt that increased attention and coordination has occurred between manufacturers and the government to begin addressing this problem, clearly more can be done to mitigate these shortages in the future.

Drug supply shortages are not new. Any product that involves complex manufacturing and distribution could face some supply challenges. What is new is the volume of shortages, the importance of the therapies that are experiencing shortages, and the challenges these shortages present to patients and caregivers. Every year since 2005, drug shortages have become more prevalent and widespread.

In 2009, there were 157 products on the FDA's shortage list, and in 2010 that number increased to 178. According to the University of Utah, which keeps track of shortages for the American Society of Health-System Pharmacists, the total number of drugs in shortage currently exceeds 275 FDA-approved therapies and continues to grow.

What is the impact of these increasing shortages? This crisis means worse outcomes for our patients, increased costs for caregivers and the government, slower medical advancement, and persistent undermining of confidence in our country's health care system.

Many of these drugs in shortage are used in current oncology treatment regimens. Not only are drug shortages impacting current treatments, they are harming future patients by delaying clinical trial results, increasing the length of clinical trials and raising costs for research organizations.

Our Federal payer system is also bearing the cost of drug shortages. Clinicians are forced to scramble to find alternative treatment options for vulnerable patients, often at a much higher price for both the patient and the government. According to research by Premier, drug shortages could cost U.S. hospitals at least $415 million annually. This is because more expensive substitutes are often needed, intermediaries significantly mark up the price of these

drugs, and there are additional labor costs associated with finding these alternative solutions.

So what is causing this crisis? Well, this is clearly a complex issue. I believe we must look at the impact of Federal programs on the generic injectable market. Seventy-four percent of drug shortages involved sterile injectables in 2010. I do not believe it is simply a coincidence that shortages are disproportionately impacting products with highly complex manufacturing processes that are also some of the lowest-priced therapies, and I am not the only one to think that economic incentives play an important role in this issue.

As recently highlighted in an article in the *New England Journal of Medicine*, experts contend that Federal government pricing and rebate programs are a significant contributing factor to the current drug shortage crisis. The article also notes that there is "untapped capacity" to produce generics, but indicates that incentives to attract new entrants would be required to create redundancy in the market.

Now, Mr. Chairman, I ask unanimous consent that this article be included in the record.

The CHAIRMAN. Without objection.

[The article appears in the appendix on p. 57.]

Senator HATCH. Current pricing structures have been very effective in driving generic utilization. However, they may not fully capture or reward the costs associated with the complex development and manufacturing of injectables, as opposed to the more straightforward manufacturing process in the pill market.

The current situation is simply unacceptable, and we must act to address this growing crisis. As most of my colleagues know, I am working on a solution that will continue to improve coordination between manufacturers and the government that also addresses some of the Federal price control and rebate structures that prevent the true costs of bringing these important medicines to patients from being adequately addressed.

Now, I urge my colleagues to join me in working to solve this problem in the very near future. Senator Baucus, I want to thank you again for convening this hearing today. I do look forward—and I am glad I got here before Dr. Thompson finished his remarks—to hearing from our witnesses and to having a serious discussion about the steps we need to take in order to address these very serious problems. This is really a crisis, in my opinion.

Thank you, Mr. Chairman.

The CHAIRMAN. You bet, Senator. Thank you very much. Thanks for your deep interest, including your legislation. I think your bill and others are going to help us find a solution. Maybe not a total solution, but they will move us in the right direction.

[The prepared statement of Senator Hatch appears in the appendix.]

The CHAIRMAN. Dr. Cobb?

STATEMENT OF DR. PATRICK W. COBB, ONCOLOGIST, FRONTIER CANCER CENTER, BILLINGS, MT

Dr. COBB. Chairman Baucus, Ranking Member Hatch, members of the committee, thank you very much for giving me an oppor-

tunity this morning to talk to you about the impact of the drug shortage crisis on cancer patients throughout the United States.

I have been a private practice oncologist in Billings, MT for the last 16 years. Every day, patients come to me asking a simple but critical question: can you help me? For most of my career the answer has generally been "yes," that is, up until now.

The recent shortage of generic chemotherapy drugs has significantly limited our treatment options and in many cases has made treatments much more expensive than they have to be.

I want to share the stories of two patients to illustrate the problems we are facing. Jerry is the father of two young children who came to the emergency room complaining that his nose would not stop bleeding. Ultimately, the work-up showed that he had acute leukemia, which is a deadly disease, but one that is very curable with chemotherapy.

The standard treatment involves a generic drug called cytarabine, but that drug is in very short supply. We were able to find enough cytarabine to get Jerry through his first cycle of therapy, but now the problem is that his condition demands a significantly higher dose of cytarabine to cure his disease, and we are not sure we will be able to find enough cytarabine to complete his treatment.

So what do I tell Jerry, his wife, his parents, his kids? Well, Jerry, with proper treatment you have a pretty good chance of surviving your leukemia, but I do not know if I can find enough cytarabine to treat it. We may have to consider an alternative treatment, but that regimen may not have the same track record of cure. As you can imagine, this is not a conversation that any oncologist wants to have with a cancer patient.

Now another patient, Donna, who is a senior who is covered by Medicare, was recently diagnosed with colon cancer. She had surgery that removed the primary tumor, but the pathologist found that the cancer had spread to three lymph nodes, which puts her at increased risk that the cancer will return.

Now, by giving her chemotherapy post-operatively, I can decrease the odds that the cancer would come back and significantly improve the likelihood that she will be around to watch her granddaughter graduate from high school in 3 years.

Donna's chemotherapy regimen involves leucovorin, a generic drug that costs Medicare about $35, and Donna's 20-percent copayment is about $9 per treatment. Unfortunately, leucovorin is another one of these drugs that is in short supply. If we cannot find enough leucovorin, I have to use Fusilev, a brand-name drug. The problem is that Fusilev is significantly more expensive for both Medicare and for Donna. So, if we have to use Fusilev, it costs Medicare over $24,000 more, and Donna's share of this is an extra $6,000 more for the 12 cycles of treatment.

So what do I tell Donna? Sorry, Donna, but I have to substitute a drug that is significantly more expensive. It is going to cost you an extra $500 per treatment, even though it is not any more effective than the cheaper drug. Again, a very difficult conversation to have with a patient.

I speak with oncologists from across the country on a regular basis, and I can assure you that these patients' stories are not

unique to Montana. Cancer treatment is being delayed, changed, and, in some cases, even stopped every day in the United States.

When I am faced with a cancer patient, I have to determine the origin of the disease before I implement treatment. In analyzing the drug shortages, it is clear that there are a lot of causes, but it is also clear that the root cause is economics. It can be tracked back to the way Medicare Part B reimbursement was changed in the Medicare Modernization Act of 2003. Although I agree with the intent to better balance payments for cancer drugs and services, there have been some unintended consequences.

The first consequence has been the closing of cancer clinics and the consolidation of clinics into the more expensive hospital setting due to Medicare reimbursement cuts to both drugs and services. The Medicare reimbursement system is based on ASP, or the average selling price of a drug, which acts as a form of price control. As a result, we have cases where some drugs actually cost a cancer clinic more than Medicare reimbursement pays.

The drug shortage crisis is another direct consequence of the MMA. Lowered payments for generic drugs have resulted in fewer generic manufacturers. Now, at first blush, falling prices should look like a great thing for Medicare and for patients.

But the problem is that there are now only a few manufacturers who are willing to produce sterile injectable chemotherapy drugs for what can be less than $1 per vial. Any manufacturing, regulatory, or quality problem is then magnified, and this leads to shortages when there are so few producers.

We have to treat the underlying cause of the drug shortages, not just the symptoms. I believe that the drug shortage problem is a direct consequence of the reimbursement system that was set up by the MMA, and it has to be changed.

It is critical that Congress move quickly to modify the Medicare reimbursement system, certainly not to cut reimbursement any further as some have proposed, and to create appropriate incentives for generic manufacturers. The lives of cancer patients hang in the balance.

Thank you very much for listening.

The CHAIRMAN. Thank you, Dr. Cobb.

[The prepared statement of Dr. Cobb appears in the appendix.]

The CHAIRMAN. Dr. Gottlieb, you are next.

STATEMENT OF DR. SCOTT GOTTLIEB, RESIDENT FELLOW, AMERICAN ENTERPRISE INSTITUTE FOR PUBLIC POLICY RESEARCH, WASHINGTON, DC

Dr. GOTTLIEB. Good morning, Chairman Baucus, Ranking Member Hatch. Thank you for the opportunity to testify today. I am a resident fellow at the American Enterprise Institute and a practicing hospital-based physician.

I have seen the effects of these shortages first-hand in my clinical practice, and, as a former FDA Deputy Commissioner and a former senior official at CMS, I have also seen the genesis of some of the policies that have contributed to these challenges.

I do not believe there is a discrete set of policy problems that has created these shortages, nor a single measure that can mitigate these woes. But I would urge this committee to focus attention on

those elements that are in its direct purview: policy failures that reappear as common factors in many of the shortage episodes.

The first issue is mechanisms that make prices sticky, limiting profitability and precluding investment in new supply and more efficient manufacturing. The second factor is regulatory challenges that have made the production of these drugs safer and more reliable, but in some cases substantially more expensive at the very time the policies have made it hard for producers to take and sustain price increases. The third category is market structures that prevent firms from being able to earn appropriate returns when they invest in key improvements in manufacturing.

The most significant of these issues in these markets is that pricing is sticky. These drugs are often very cheap, sometimes just several dollars for a dose. As a result, manufacturing costs end up comprising a big proportion of the overall price of the drug.

When demand for these drugs increases or when the cost of developing the medicine rises, manufacturers cannot take and sustain price increases to make up for these events. This makes it hard for firms to make the long-term investment needed to stand up new manufacturing facilities or upgrade existing facilities to produce more supply.

One contributor is the way that Medicare reimburses these products according to ASP, which is at least 6 months old at any given time. This means even if a generic firm raises its price to reflect increased production costs, Medicare will not pay the new price until about 6 months later. As a result, the producers of the drug would be under water for months at a time.

Another issue is the way that Medicare lumps all the drugs into the same billing code. This means that the price paid ends up reflecting the terms of the lowest-cost producer, creating pressure to shave down production costs. Once ASP falls to a new low, it is hard for it to rise again because of its stickiness. Firms end up in a race to the bottom on manufacturing costs.

This race to the bottom on manufacturing can work reasonably well in producing significant savings when it comes to products that are easy to manufacture, like pill forms, but it creates risks in markets like sterile injectable drugs where manufacturing is not a trivial affair.

The regulation of pricing is made more problematic by the fact that production costs have been increasing, owing to more stringent regulation of manufacturing. The FDA has legitimate concerns, but the fact is, regulatory oversight has been sharply tightened over a short period of time. These low-margin producers cannot easily meet the new mandates.

To fix the problems, we should lift price controls when it comes to critical injectable drugs that are generic, and take steps to provide companies with incentives for making manufacturing upgrades that can lead to a more stable and scalable production.

First, Medicare should move away from ASP and pay for these drugs according to a more flexible, market-based price that could adjust to market conditions. One consideration is to reimburse these drugs based on the price paid by wholesalers, the wholesale acquisition cost.

Congress might also consider allowing ASP to be re-set in some fashion for drugs approaching a shortage or drugs that are considered critical and prone to shortage. These drugs should also be exempt from price control schemes that distort market prices and reduce incentives to invest in new production. This includes the 340B program.

Medicare can also allow these drugs to have individual billing codes rather than paying for each class of drugs according to the same code. We also should give firms a financial incentive to invest in new IP that can improve manufacturing characteristics of generic drugs.

Finally, we need to view production capacity for critical drugs as a national strategic asset. In the past, government approached similar issues with targeted incentives such as tax credits to encourage development in more domestic manufacturing capacity. The episode with flu vaccine provides some good examples of how we might mitigate the current shortages.

To resolve these shortages in the short term, we should focus on the existing manufacturing capacity that is available but has been taken offline as a result of regulatory findings.

In the long run, the only way to improve the availability of these products is to make it possible for firms to keep pace with rising production costs and to invest in manufacturing and enable a more stable and more scalable supply. We need to reform the policies governing how these products are priced if we are going to attract new investment into these areas.

Thank you very much.

The CHAIRMAN. Thank you, Dr. Gottlieb.

[The prepared statement of Dr. Gottlieb appears in the appendix.]

The CHAIRMAN. Dr. Conti, you are batting clean-up here.

STATEMENT OF DR. RENA CONTI, ASSISTANT PROFESSOR, UNIVERSITY OF CHICAGO, CHICAGO, IL

Dr. CONTI. Thank you. Good morning. Chairman Baucus, Senator Hatch, and members of the Senate Finance Committee, it is my honor to speak to you today. I am an assistant professor of health policy and economics at the University of Chicago, and my work focuses on the regulation of the pharmaceutical industry.

In economic terms, a shortage exists when, at any given market price, quantity demanded by purchasers exceeds the quantity that is supplied by firms. In a competitive industry, profit-maximizing firms would raise their price, consumers would be willing to pay this increased price for necessary drugs, and over time suppliers would increase the quantity supplied, eventually eliminating shortages.

It is my contention that the defining features of the drugs in short supply suggest that aspects of the supply of, the demand for, and the distribution of them may constrain competitive market behavior.

I evaluated several proposals. The use of drugs to treat disease is central to contemporary medical practice. Most drugs in short supply in the United States are to treat cancer, are physician-administered, and lost patent protection prior to 2000.

These features suggest there are four discrete aspects of the financing and organization of these drugs that have acted in concert to create the current crisis, in effect a perfect storm.

Regarding supply, firms that produce generic specialty drugs are concentrated, multinational, and produce multiple drugs across therapeutic areas. These firms drive profits from reducing manufacturing costs, but also by making drugs that have the highest revenue potential. All else being equal, we should expect firms to shift away from manufacturing drugs with low demand to higher revenue producing drugs over time.

Regarding demand, oncologists choose drugs to maximize the health of their patients to be sure; however, physicians favor newer drugs with recently established safety and efficacy profiles. In addition, Medicare's reimbursement to physicians for the administration of these drugs has declined over the past decade, putting pressure on practice revenues. These changes reward, again, the use of higher-priced drugs that offer physicians higher cost recovery, all else being equal.

Regarding distribution, drugs are purchased by providers through purchasing organizations. The discounted price and the preference for filling orders are not equally distributed across all members of a purchasing organization; rather, they are based on the members' purchase volume. Low-volume community practices are the most vulnerable to interruptions in product supply and also to higher prices.

Numerous remedies have been offered. First, proposals to increase physician payment include increasing the average sales price for selected products or switching to reimbursement from average sales price to wholesale acquisition cost, or WAC.

Empirical work suggests physicians do appear to make prescribing decisions based upon alterations in the reimbursement they receive from payers. Increased payment for drugs would reduce the strength of the incentive for physicians to prescribe the drugs at the highest cost recovery, in effect equalizing the incentive to prescribe a generic drug or brand of drug for a given disease. Firms could, in turn, raise prices.

The trade-offs of this proposal include the following: is WAC available for all drugs? Our preliminary review suggests not. Would the increase in payment to physicians generate enough revenue for firms to compensate for the increased costs incurred from increased supply? This is an open empirical question at this time. And finally, in what time frame would increased supply occur? I expect the time frame varies considerably by generic firm, but also by the drug.

Second, it has been suggested that penalties on firms could be strengthened and targeted to apply to the supply of drugs that are "necessary." This policy would force firms to invest in a limited additional capacity to manufacture specific drugs and effectively raise the firms' total cost.

Firms' compliance with these penalties is predicated on two things: first, the magnitude and timing of the penalty and the strength of its enforcement; and second, the ability of the firm to offset these penalties through higher prices.

It is likely that firms would pass these costs off to purchasers, either through higher prices among all the drugs that they make in a bundle and/or higher prices for the given drug by all purchasers, domestic and international. It is possible not all purchasers would be affected equally by increased prices.

I suggest a combined approach. Policymakers should consider ensuring that the reimbursement firms receive for the production of these drugs in short supply deemed necessary is increased; second, equalizing the incentive physicians have to prescribe equally effective branded and generic drugs. These incentives could be financial or could be other types of policies that encourage guideline-adherent practices. Finally, assessing the benefits of the cost of enacting penalties that compel generic firms to invest in the capacity to produce an adequate supply of any necessary drug in the case of domestic shortages or national emergency, irrespective of the purchasing channel for which they obtain their drugs.

Thank you.

The CHAIRMAN. Thank you, Dr. Conti.

[The prepared statement of Dr. Conti appears in the appendix.]

The CHAIRMAN. I apologize, but the Supreme Court, in a few minutes, is going to hear oral argument on a case that directly affects the State of Montana, and I am going to go over and listen to that oral argument. I am going to have to turn the hearing over to Senator Hatch. But thank you all very much, and I will have many questions. Thank you.

Senator HATCH. Well, thank you, Mr. Chairman. I hope it works out well for Montana.

The CHAIRMAN. I am going to be sending my vibes up to all the members of the court system. [Laughter.]

Senator HATCH. I can imagine.

Well, we are delighted to have all of you here and to have your testimony. Let me just ask this question. Since the government indirectly impacts drug pricing through reimbursement to providers, if we raise reimbursement for drug acquisition, how will we know the profits will ultimately reach the manufacturer to spur additional investment? We will start with you, Dr. Thompson, and anybody else who would care to remark about it.

Dr. THOMPSON. Sir, I do not know if I have a great answer for that question. We have really looked at, over the last 10 years, a lot of the manufacturing drivers that have influenced shortages and have been very interested in the new economic arguments that have resulted. So perhaps I will pass that question on to others who might be able to give a more direct answer.

Senator HATCH. All right. Does anybody else care to take a crack at that?

Dr. GOTTLIEB. This is a very competitive market. If the manufacturers have the capability to take price increases, they will. The only way—if you allow the ASP to become unbundled, if you will, so it is not sticky anymore, the only way for that price to ultimately be reflected in the marketplace is for the manufacturer to take a price increase that ultimately flows through to what the doctor gets reimbursed, or the provider gets reimbursed, for administering that drug.

But if you look at the other entities that are in the supply chain, it is also very highly competitive, if you look at the Group Purchasing Organizations and the other Pharmacy Benefit Managers that handle these drugs, the specialty pharma companies. So there is no reason to believe that they are going to be able to capture that margin. It is going to flow back to the manufacturer.

Senator HATCH. All right.

Dr. CONTI. I agree.

Senator HATCH. You are pretty much in agreement.

Let me ask you this. While shortages are not new, they have gotten progressively worse over the past several years. Now, is it not true that when reimbursement was substantially higher, we were not experiencing such severe shortages in the marketplace? Doctor?

Dr. COBB. That is true, Senator. Back in 2003, before MMA was implemented, there were not very many chemotherapy drug shortages. There were only about three at that time. After ASP was implemented, prices on some of these drugs plunged. For some of them, they dropped by more than 50 percent for a group of 13 of those drugs. By last year there were 23 chemotherapy drugs that were short. So that is what led to my conclusion that the root cause of this is the economics and the reimbursement system that was set up by MMA for generic drugs.

Senator HATCH. Okay. Yes, go ahead, Doctor.

Dr. CONTI. Thank you. In addition, consolidation in the generic industry has increased substantially over this period, and that also increases the cost pressure for manufacturers to really drive down the cost or the efficiency of producing these therapies, and also to shift away from lower-margin, low-demand drugs to much higher revenue potential drugs for the firm.

So it is not just incentives on the physician to really shift away from generic, cheap drugs that they get reimbursed for, but it is also pressure from the manufacturers to produce other types of drugs.

Dr. GOTTLIEB. That consolidation also increases risk because, if you have a manufacturing problem, because the manufacturing has been consolidated as well, you can knock out many lines of many different drugs by taking out a single facility.

I think there are two sides to this equation. At the very time that we implemented policies that drove down the reimbursement for these products, over that same period of time we implemented policies that dramatically increased the cost of production of these products, and the equation does not line up anymore, if you will.

I think as a policy matter, if we want to implement tighter and more stringent regulatory scrutiny of the manufacturing of these products, we are going to have to pay for it. That is what we have seen in this market in recent years. I would estimate that, if you looked at the top five manufacturers, probably about 15 percent of the available manufacturing capacity is now currently offline and being remediated. Now, that is a good component of your shortage right there.

Senator HATCH. Well, thank you for this.

Some have questioned the impact of changing reimbursement for generic injectables on alleviating drug shortages, yet you disagree. Now, this is for Dr. Cobb. You disagree, as do contributors to the

New England Journal of Medicine and Dr. Zeke Emanuel, another noted oncologist and former senior official of the Obama administration.

Can you explain in more detail, Dr. Cobb, how changes to Federal reimbursement policies could create additional capacity and supply in the market for these drugs? And if anybody else would like to answer, that would be fine too.

Dr. COBB. Yes. I think one of the thoughts is that branded chemotherapy drugs have taken over the market. That is really not the case. If you look at the unit sales of generic drugs, those have actually surpassed the sales of branded drugs. And for a lot of these generic drugs that we are talking about being short on, there just is not any other alternative. I think that is a big problem for the generic drugs, because there are very few instances where you can substitute a branded one for a generic one, so sometimes that does not always apply here.

Senator HATCH. Yes, Doctor?

Dr. CONTI. I would add that shortages increase the time cost for physicians to find a work-around solution, and those time costs do not bind equally across all providers in the marketplace. What I mean by that is, community oncology practices and practices that are very limited in terms of their resources are likely going to be the ones that are going to be most affected by the shortages. They are going to be most unable to work around a shortage to try to find another potential therapy in a short period of time to treat a given patient.

Senator HATCH. All right.

Doctor?

Dr. THOMPSON. And I think something else has to be looked at. MMA still may just be coincidental. We have been tracking this for over 10 years, the fact that more drugs have gone off patent over that time period and made it more lucrative for manufacturers to enter other businesses. Fifty-four percent of shortages are manufacturing problems, many of these longstanding.

So we believe, in addition to looking at the impact of reimbursement, looking at ways to provide incentives to manufacturers to get these downed production lines back online to increase capacity to produce these drugs is a very important area to look at, in addition to the economic factors related to reimbursement.

Senator HATCH. Well, thank you.

Senator Bingaman, we will turn to you.

Senator BINGAMAN. Thank you very much. Thank you all for your testimony.

Let me just follow up on that last comment. Are there some specific actions that you think the government should try to pursue to create incentives for manufacturers to keep active in producing some of these drugs that no longer are on patent and no longer bring in the high revenues that they once did? Dr. Thompson, maybe you could answer first. Yes?

Dr. THOMPSON. Yes. Well, as we mentioned, helping manufacturers resolve some of these problems in their production process is one factor. As I mentioned in my testimony, looking at economic factors or looking at tax incentives for manufacturers is—well, we are not in a position to describe what those are.

I think manufacturers are in the best position to say what would be helpful to them, but we think some sort of tax incentive should be looked at for manufacturers to stay in this business.

Senator BINGAMAN. Do any of the rest of you have a thought about that?

Dr. CONTI. I do. I think that the solution or potential solution requires both a carrot and a stick. And what I mean by that is that we absolutely must ensure that firms receive additional monies for the production of drugs in short supply, and in particular we need to think about what drugs in short supply we would want to recommend that they make. I would suggest that defining therapeutically necessary lines of therapies seems to be an important ingredient to this.

Second, I do think that increased incentives also need to be jointly enacted with some penalties that compel generic manufacturers to invest in the capacity to produce an adequate supply of the drugs that are deemed to be necessary in the marketplace, and that could include both penalties on the generic firms, but also penalties within the generic firm and purchasing organization contract.

Dr. GOTTLIEB. Two thoughts. I do think that the idea of some kind of incentives to develop domestic capacity for manufacturing these products is something that is important to look at. When we did that with respect to flu vaccine, we got companies to build many more facilities in the U.S. to manufacture a flu vaccine, and we looked upon that as a strategic national asset.

I think the same thing applies to a lot of these drugs. These are critical need drugs that are in short supply worldwide, and in many cases the manufacturing capacity for these drugs is not domestic, and that could become a problem down the road.

The other thing longer-term is, I think that we should think about whether or not there is a way to develop a construct that would allow companies to develop intellectual property around making the kinds of manufacturing improvements that they are now being prodded to do by the Food and Drug Administration, manufacturing improvements that make the manufacturing process more reliable, more scalable.

If companies could make those manufacturing improvements and develop some IP around it, even if it did not change the characteristics of the drug, if they could make claims in labeling as to what kinds of improvements they made, maybe that would allow for some kind of pass-through payments, whether it is something that is a pass-through payment under a diagnosis-related group, or maybe guaranteed purchasing by certain government programs like VA, but it would create an incentive structure for developing intellectual property around improving the manufacturing process and making it more reliable.

Senator BINGAMAN. The suggestions that several of you made that we change the reimbursement policies of Medicare in order to facilitate or solve the problem of these shortages, is it your view that the statutes need to be changed in order that Medicare have that authority or that Medicare has that authority today and can go ahead and make these policy changes, reimbursement policy changes?

Dr. COBB. As far as a policy is concerned, I am not really sure legally how that would happen. But for us, we think that scrapping the ASP model for reimbursement for generic drugs is really important. The problem is that the ASP system for generic drugs has turned generic drugs into commodities, but chemotherapy is not really a commodity because—if you look at pork bellies, if you run out of pork chops, you can reasonably substitute a hamburger. But, if you run out of cytarabine, there are no substitutes for this. So chemotherapy has to be taken out of this commodity-based pricing that is a result of ASP. I think that is really important.

Senator BINGAMAN. Do any of the rest of you have a thought on that? My time is up at any rate. Senator Hatch, thank you.

Senator HATCH. Senator Wyden?

Senator WYDEN. Thank you, Senator Hatch. And Senator Hatch, let me just commend you, because you and I have worked together often on these kinds of issues. I think once again you are headed in the right direction, and I want you to know I would like to work with you again on this important area.

For all of you as witnesses, you may know at the Oregon Health Sciences Center we are very proud to have Dr. Brian Druker, who developed Gleevec. It is the breakthrough drug, of course, that targets specific cancer-causing molecules.

I have come to conclude after talking to him and some of his patients that there is absolutely no way to get a solution here without overhauling the reimbursement process. There are other issues that are important, but that is right at the center. I can only imagine, Dr. Cobb, what it is like for you and stellar physicians like Dr. Druker to tell patients that these life-saving treatments that used to be available are no longer available. It is a disgrace that, in a country as good and strong as ours, that goes on every single day, and that is what we have to solve. I think, as I have indicated, Senator Hatch is headed in the right direction.

Now, let me see if I can get in a couple of questions. I want to talk with you to start this off, Dr. Conti, because, with cancer drugs, reimbursement issues are a special challenge because there is an issue not only of the amount of the reimbursement, but also who gets the reimbursement.

With generic cancer drugs, for the most part, the person purchasing the prescription is the doctor as opposed to the patient. So if you could, just walk us briefly through how increasing the reimbursement of these drugs—and they will be Part B drugs, outpatient drugs, for example, to seniors—to the doctor is going to provide greater incentives for a manufacturer to produce the supply.

Dr. CONTI. Thank you. That is an excellent question. There is no doubt that physicians do appear to make prescribing decisions based on the alterations in the reimbursement for these therapies. And remember, physicians both receive reimbursement for the cost of buying the drug, but also for administering the drug to their patient. That is a separate reimbursement line that physicians receive.

It is clear that increased payment for these drugs would also increase the incentives to choose more carefully between generic and branded therapies. However, I am unclear how an increase in payment to physicians would be immediately passed through to manu-

facturers unless manufacturers increased their prices in concert and group purchasing organizations would allow these increased payments to physicians to flow directly through to manufacturers.

Senator WYDEN. I want to ask one other question, Senator Hatch. But I think this is certainly one that we will want to look at on a bipartisan basis, because I had a number of cancer physicians and companies ask me about the relationship of the physician and the manufacturers, and I think it is one we are going to have to look at.

Now, let me ask you one other question, Dr. Conti. Maybe some of the others of you would like to chime in on this. In effect, what Congress would be talking about, and you all refer—at least three of the four of you in your testimony—to higher reimbursements in instances particularly with respect to cancer care where the need was urgent or necessary. So in effect, the Congress would almost be talking about a trigger that would, in effect, give higher reimbursements for drugs that were "urgent" or "necessary."

I have to think the American people are going to say, holy Toledo, how in the world is the U.S. Congress going to figure out how to make decisions about these life-saving drugs and set itself up as the authority to make judgments about drugs that are "urgent" or "necessary"? And certainly a patient is going to say, when it is my case, you bet it is urgent there, Congressperson.

Why don't we start with you, Dr. Conti? This, to me, is sort of the $64,000 question. Somebody is going to have to be part of guiding the Congress and the country through what really constitutes how you get reimbursement in those areas that have been declared to be urgent and necessary.

So we will start with you, Dr. Conti, and just go down the row. I would like to hear how you all would go about making that kind of judgment, because certainly Senator Hatch and legislators who are trying to work on a bipartisan basis are going to have to wrestle with that issue.

Dr. Conti?

Dr. CONTI. Thank you. Clearly, information regarding the availability of therapies and its distribution geographically and by physician type is critical to understanding, to really anticipating and alerting the American population regarding the possibility of a shortage of a medically necessary therapy. There are other existing systems in place that are overseen by the FDA that monitor shortages for other medically necessary drugs, including plasma protein therapies.

In terms of defining "necessary," I think that there are at least three important features. The first is, I think, that you would need a medical panel of experts to really define what we mean by "medically necessary." However that is possible, we have other types that exist within CMS, but also within FDA already.

First, it would probably have to be used in a fatal condition. Second, there would have to be limited or no therapeutic substitutes. Third, if there were any therapeutic substitutes, there would have to be no, or very limited, head-to-head trials establishing both safety and efficacy in limited patient populations, but also in the general patient population that could be affected by these shortages.

Senator WYDEN. Any other witness? I know my time is up, Senator Hatch. Are there any other witnesses who would like to help counsel the Congress how to wrestle with the definition you want us to establish?

Dr. GOTTLIEB. You could move all the sterile injectable drugs into a new reimbursement scheme. In the context of cancer, we are only talking about, I think, a few dozen drugs. So we are not talking about a huge subset of drugs, and most of them are low-priced drugs to begin with.

Senator WYDEN. So you would draw the line—this is an important point—on an urgent drug, for example, as a cancer drug and say that it is life-saving?

Dr. GOTTLIEB. Well, I am not looking at it in terms of whether it is an urgent drug or not. I am looking at it in terms of if it is an expensive drug to manufacture, where there needs to be some margin built in for the allowance of companies to invest in better manufacturing, especially in an environment where the regulatory burdens are increasing. So that applies to all the sterile injectable drugs. I would treat them differently as a category of drugs. I think we are talking about a few hundred drugs in total.

In response to your last question, just quickly, when we talk about moving away from the ASP pricing scheme for these drugs, we are not talking about increasing the reimbursement to the doctor per se, we are talking about allowing the companies to take price increases that would not then leave the doctor under water.

There are two reasons primarily why the manufacturers right now cannot take price increases. One is, their GPO contracts. I am sure Congress does not want to get into the business of regulating their contracting. But the other is that, if they take a price increase, at least on the outpatient side, they are going to leave the doctors under water for 6 months.

Since they make very little money on these drugs anyway, and in many cases these drugs are loss-leaders, the last thing they are going to do is leave customers under water for 6 months and incur the wrath of their customers. They would rather just either take the loss or get out of the business altogether.

Senator HATCH. Senator Cornyn?

Senator WYDEN. I know my time is up. But, Senator Cornyn, could those two just finish then on this question of how we make judgments about what is urgent and necessary?

Dr. COBB. I think the idea of treating sterile injectables as a class makes a lot of sense. It gets out of the value judgments on which drug is critical and which is not. But for cancer patients, it is almost all of the generic injectables.

Dr. THOMPSON. Senator Wyden, that is a very good question. We have been tracking this issue for a long time. Drug shortages are all over the place, and I think one thing you are pointing out is, this is a very broad category. Oncology drugs are obviously the ones that concern us the most just because of the implications. But you are looking at drugs like heparin, anesthetics that are used in the OR suite, drugs that are used for feeding patients parenterally.

So it is really a moving target. We think there is going to have to be more transparency in the entire supply chain so we can create some predictive models, because creating the perfect list of

medically necessary drugs is virtually impossible. We have been doing this for a long time, and it is just very hard to do.

Senator WYDEN. Thank you, Senator Cornyn, for letting me impose on your time.

Senator HATCH. We will go to you, Senator Cornyn.

Senator CORNYN. I share Senator Wyden's skepticism in the expertise or the competence of Congress to micromanage the manufacturing and pricing of generic sterile injectable drugs. I just think it is crazy for us to try to get into the nitty-gritty details of it.

I wonder if there are lessons to be learned from other very successful programs under Medicare, like the Medicare prescription Part D program, which admittedly is different because it is prescription drugs, readily available. But rather than price fixing, which seems to be the chronic problem that Congress has when it comes to health care, trying to set prices, we see the discipline of an actual market take place.

Amazingly, the price of Medicare Part D now is some 40 percent under original projections because people have choices, they have transparency, they get better service because there is competition, and the overall quality is very high.

So I wonder, are there lessons we can learn from what we have succeeded in and those areas where we have failed, where we have seen manifest shortages, that should guide our deliberations in how we go forward? Dr. Gottlieb, why don't you start?

Dr. GOTTLIEB. Well, I think ideally we should move Part B altogether into Part D and allow these drugs to be acquired in a competitively bid market. I think there are a lot of complexities to doing that. You are going to need to use some of the savings that you would accrue from that, savings that would accrue because you would have these drugs now tiered and pre-authorized, and all the mechanisms that have driven down prices and utilization in the Part D scheme would now apply to the Part B drugs, and that would increase certain savings. You would have to use some of that savings to offset the increase in premiums that patients would experience, the increase in co-pays that they would experience.

You would have to find a way to reimburse the doctors directly in an honest fashion for the infusion of those drugs rather than doing it through an arbitrage on the spread of the drugs. But the whole system would be far more transparent and I think competitive than allowing these drugs to be continued to be reimbursed in the Part D scheme. So, I agree with you, Senator.

Senator CORNYN. I would invite all of you to, even after this hearing, send us your ideas, your best ideas about how we might be able to do that. We could certainly learn a lot from you.

I know that under the Medicaid rebate programs that exist currently, the Medicaid enrollees must enter into rebate agreements with the Secretary of HHS on behalf of the States, and under those agreements pharmaceutical manufacturers provide State Medicaid programs with rebates on drugs for Medicaid beneficiaries.

Of course, that is designed to make sure that the States, and thus the Medicaid beneficiaries, pay the lowest price that manufacturers offer for those drugs. But I wonder whether that creates the sort of distortions that we are talking about here and the disincentives, it strikes me.

Dr. Cobb, would there be some way—and this is a little bit different twist over my lead-in—for example, if there was a stockpile of a drug you needed in Billings, MT in San Antonio, TX, would there be some possibility of a clearinghouse that either the FDA or someone else could provide where physicians who were looking at maybe malapportionment or distribution bottlenecks could access those drugs? Would that be sort of an easy way to at least deal with some of this problem?

Dr. COBB. I think that is an interesting concept, to have a stockpile that the country has. The problem with sterile injectables is that they out-date and they become unusable. So, as a practical matter, it would be very difficult to have a certain warehouse of medications that you can just keep as a backlog.

I think ultimately it would probably end up being more expensive. I think a better choice would be to have the market reflect the actual cost of manufacturing these drugs, to scrap the ASP model of reimbursement because that acts as an artificial price cap on things.

Senator CORNYN. All right.

Dr. Thompson, do you have any comments on that?

Dr. THOMPSON. We, similar to Dr. Cobb, have never thought stockpiling would be feasible, just given the fact that——

Senator CORNYN. And let me just clarify. It was not an intentional stockpiling I was referring to, it was just basically a maldistribution.

Dr. THOMPSON. Yes. I think from conversations we have had with clinicians and our members, there is a lot of sharing that happens in the supply chain. The problem is, it is finite. Everybody is dealing with shortages. One organization may have more product, but it is going to be in short supply eventually when you just absolutely have nothing coming off the manufacturing lines. So there are a lot of creative things that are happening out there now, but when the drug is not available from the manufacturer, at some point it is limited.

Senator CORNYN. You mean, there are even creative things happening without Congress directing it? [Laughter.]

Dr. GOTTLIEB. I would just add to that, a lot of the reallocation that does take place in the marketplace is, the small distributor is reallocating product, and oftentimes they have to acquire the product at a much higher price than what GPO might acquire it at.

I raise this just because there has been a lot of discussion about the so-called gray market and profiteering, but a lot of those small distributors that are acquiring the drugs at higher prices, and significantly higher prices, and then selling them, obviously at higher prices as well, are providing an important market-clearing function.

Senator CORNYN. Thank you. My time is up.

Senator HATCH. Thank you, Senator.

Senator Cardin?

Senator CARDIN. Thank you, Mr. Chairman. And let me thank all of our witnesses. I think this is an extremely important hearing.

Let me just underscore the urgency of what we are dealing with here. I have gotten a lot of letters and calls from constituents, and I am sure all my colleagues have gotten the same. Let me just

quote from one of my constituents who said, "My doctor put me on Doxil and carboplatin to try to get rid of some tumors associated with ovarian cancer that has been hanging around. I had four treatments with both drugs and was responding very, very well. I have now missed three doses of Doxil, due to the shortage, and I am treading water with the carbo, but I am frustrated that I am no longer making the process towards remission." So we talk about the number of drugs that are in shortage, but each one affects some person and some family.

I would also like to bring up the impact that the shortages are having on clinical trials. I represent Maryland, which is home to the National Institutes of Health. When they do their cancer trials—and they have about 150 cancer trials that are currently being conducted through NIH—they do not use a placebo, they use the standard of care drugs versus experimental drugs. Of course, the shortage of the standard drugs is hindering scientists' ability to make progress on clinical trials, and this affects the whole health care system.

So I really want to get to the urgency of what we are dealing with. I understand your suggestions on a lot of the pricing issues, and you are absolutely right to put that on the table. We have to get this right. But I want to concentrate on what we can do in the immediate future to deal with the concerns that have been legitimately raised by our constituents that their care is being compromised. They look to us to do something about that.

So what can we do now to alleviate these shortages so that people can get the care that they need?

Dr. GOTTLIEB. Well, I know it is not the purview of this committee, but there is a lot of manufacturing capacity that is currently offline and undergoing remediation by the FDA. I think getting a sense of how much capacity has been taken out of the market would be important, and you can simply send letters to the top five manufacturers and ask them how much of that capacity is down.

But making sure that that gets remediated as efficiently as possible and is brought back online, with FDA working with the manufacturers as quickly as possible, is extremely important. There probably are steps that we could take to help the regulators make sure that they have the resources they need to get those facilities back online.

In the near term, meaning the next 6 months, I think that that is all we can do. I think a lot of the discussion today was around, how do we fix the market failures that permeate this area for the longer term? But in the near term, I think all we can do is try to get the production facilities that are down back online.

Senator CARDIN. Are there any other suggestions for an immediate fix?

[No response.]

Senator CARDIN. HHS has considered emergency imports of some of these drugs. Do you all support that?

Dr. COBB. I think in certain cases where the drug is just not available, especially the example I gave for cytarabine, where there are no substitutes for that. So, if there is not enough manufacturing capacity in the United States to make enough to take care

of the demand, then we have to get it from someplace else. So that may be something to look at.

Dr. CONTI. Also, my understanding is that anticipated shortages in Canada have been alleviated by short-term purchases of drugs in short supply from other places, notably Australia. I think the real down side to that is just concerns about perishability and drug safety in transporting them overseas.

Dr. GOTTLIEB. There are also differences in the formulations of drugs sold overseas versus the United States. For example, when there was a shortage of propofol, FDA authorized some limited importation of a product from Europe, a similar product, but it was not the same product, and did not have the same ingredients in it that prevented propagation of infection with the product. So doctors were using a product that they thought was interchangeable but in fact needed to be used under different sterile techniques than the product they were used to using. So importing the drugs is not a panacea.

I think it is going to create its own risks. Canada, for that matter, gets a lot of their sterile injectable drugs from the same manufacturing facilities that we get ours from, so they have experienced some of the same shortages that we have. I suspect if we go wholesale trying to acquire these drugs overseas, we are going to find pretty quickly that those facilities suddenly become unavailable to us, if they are not nationalized. So it is going to create other problems.

Dr. CONTI. They have anticipated shortages, but apparently they actually have not experienced true shortages in the way in which we have.

Dr. COBB. And I think this is a very short-term fix, what you are talking about. I mean, ultimately we have to fix the underlying problem, which is that there is not enough incentive for generic drug manufacturers to make these drugs.

Senator CARDIN. And I prefaced my question by acknowledging that, and I agree with you. But I just would point out the urgency of this issue. I understand the risks of importation, but it seems to me that those could be dealt with in the short term.

If that is the best alternative available, it is better than a patient going without the drug and not making any progress in treatment. We need to have greater cooperation as we try to fix the urgent issues that we have right now, and then deal with the supply chain for the future that we all know needs to be corrected.

Thank you, Mr. Chairman.

Senator HATCH. Well, thank you, Senator Cardin.

Let me just say that I have an emergency in my office I am going to have to go to, but I want to personally thank each one of you for being here. You have been very helpful to us. We intend to solve this problem, or at least do what the Congress can do to solve it. Sometimes we can mess them up pretty badly too, but I think in this area we can solve this problem, at least to a large degree. So we will see what we can do. We have two Senators who will continue questioning. If you will forgive me for leaving, I apologize to you.

But Senator Thune is next, and then Senator Wyden has a couple more questions. So we will have Senator Wyden wind up the

hearing, unless somebody else comes. Then Senator, if you would call on them, I would appreciate it.

Senator WYDEN. Thank you, Senator Hatch.

Senator HATCH. We appreciate all of you for being here.

Senator Thune?

Senator THUNE. Thank you, Mr. Chairman. We do appreciate your being here and your contributions to this important subject. Mr. Chairman, thank you and Chairman Baucus for holding this hearing.

Dr. Thompson, I have constituents who are health-system pharmacists and belong to your organization. Many of these constituents also work for systems that participate in the 340B program. There are folks who have asserted that the 340B program is the source of the problems in drug shortages, and yet the 340B program, I believe, only accounts for about 2 percent of total U.S. drug spending. I guess my question is, have you seen any evidence that indicates that the 340B program contributes to drug shortages?

Dr. THOMPSON. No, Senator. We have seen no evidence that the 340B program is a contributing factor at all to drug shortages, for the same reasons you note. Then we speculate that it is about 2 percent of national drug purchases in the United States and just seems like a very unlikely factor in the broader scope of drug shortages.

Senator THUNE. Does anybody else want to comment?

Dr. CONTI. Yes, I would like to.

Senator THUNE. Dr. Conti?

Dr. CONTI. It is clear that prices for some therapies are very low because of the 340B program, and essentially what this does is act to transfer money from the manufacturers to physicians and hospitals by producing very low, discounted drugs.

Eliminating the program or reducing the program would potentially, again, transfer more money to the firms, so that would potentially produce increased money for them to make more of these drugs, but it also may aggravate shortages in the short-term, as more disadvantaged or vulnerable hospitals would be forced to purchase these drugs through other contracting mechanisms and potentially face increased prices.

The key question with the 340B program is, how important is a 340B program to the overall purchasing of these sterile injectable drugs, and second, what alternative options are there for safety net providers to be able to purchase these drugs at prices that they can afford?

Senator THUNE. All right. Thanks.

Dr. Thompson, your organization maintains a list of shortage drugs. How do you determine which drugs are in short supply, and is there any interface or communication with the FDA about drugs your organization deems to be in short supply?

Dr. THOMPSON. Yes, sir, there is. There is daily communication with the FDA and the University of Utah Drug Information Program, which we collaborate with on this. What we do with the University of Utah is, we conduct a root cause analysis. As soon as we get notification, from usually a pharmacist in a hospital, that a shortage is happening, we begin a process of contacting manufacturers, contacting other components of the supply chain to find out,

to determine whether the shortage actually exists. As soon as we have identified that it does, we immediately transfer that information to the FDA Drug Shortages Program.

Senator THUNE. All right.

Let me just ask a question. This is kind of a contentious issue around here, has been for a long time. But is there any reason to believe that re-importation of drugs might help assist with the drug shortage problem? Do you see any connection there between drugs that might be re-imported if that were permissible?

Dr. THOMPSON. We do not believe that it is a solution to the problem, and we believe that it raises a lot of other potential risks associated with patient safety that concern us: unfamiliar products, different formulations, labeling differences.

There have been cases with propofol in the past few years where there was an absolute necessity to find a solution because it did not exist and it was needed in the OR suite, and there was a drug imported through an FDA process to do that. But we do not think a lot of time and effort should be spent focusing on re-importation as a solution to drug shortages.

Dr. COBB. I would agree with that. We are the end user of these drugs, and, when they come from an American firm and American distributors, we know what the pedigree is, we know that the FDA has inspected the manufacturing process, and we have full confidence in the potency and the safety of those drugs. For drugs that come from other places, we are not as sure about those things.

Senator THUNE. All right.

Dr. CONTI. This is a global business for generic manufacturers, and so there is a limited supply of the drugs that they are producing across the entire world. I think importing is just not going to solve the problem long-term, because again all it will do is, it will not increase the supply of these therapies over the entire world, it will just redistribute drugs from us to other places or from other places to us. Second, the more you increase demand for these therapies in the short term through these types of redistributions, the more the prices are going to rise.

Senator THUNE. All right.

Dr. Cobb, some of the experts on the panel today have indicated that both Medicare reimbursements and oncology practitioners favor the use of new drugs versus generics. One, do you believe that to be true? And two, if so, how much of that decision, on a practitioner level, is determined based upon the concern of supply shortages or limited quantity of perhaps an older generic drug?

Dr. COBB. Well, certainly the reimbursement situation that was put forward by the Medicare Modernization Act of 2003 has changed the practice dynamics significantly. That being said, there are not that many A-versus-B substitutions that can be made. For a lot of the generic drugs that are out there, there are no brand-name substitutions.

The example that I gave of the patient with the colon cancer, where you can substitute Fusilev for leucovorin, that is more the exception rather than the rule. The same thing goes for brand-name drugs. Oftentimes there are no substitutions for this. For instance, for Herceptin, there are not any generic forms of Herceptin or anything that works like that. So the economics do play a role.

I mean, I run a small business. I hire and employ 65 people in Montana and Wyoming. It does factor into it, there is no question, but the decision comes up less than you would think.

Senator THUNE. My time has expired. Thank you, Mr. Chairman.

Senator WYDEN. Senator Grassley?

Senator GRASSLEY. Thank you very much. I have quite a background for one simple question. Maybe it is not simple, but one question I want to ask. But let me give you the background, and then any or all of you who want to can tackle it.

First of all, this is a very important hearing because I have been hearing from providers back in Iowa throughout the year about our drug shortages. It is clear that there is a problem, and I wish the solution was very clear. I think what we have here is a comedy of errors of well-intentioned policy leading to unintended policy outcomes.

According to a recent report from IMS, the vast majority of drugs that are on the shortage list are generics and injectables. These are drugs that would be reimbursed under the Medicare ASP system. The ASP system was put in place in the Medicare Modernization Act of 2003 to combat widespread price gamesmanship of Medicare Part B.

In 2005, the Deficit Reduction Act expanded the best price rebate to Part B drugs. We have also seen a dramatic increase in 340B institutions in the last 5 years taking advantage of that low-price regime.

Finally, the patent system encourages drug manufacturers to rush into the market when a drug comes off patent, and then the market drives the price to the bottom. These well-intentioned policies to drive costs down for the government as a payer have led to very unintended policy outcomes.

These policies have changed the way the market operates for generic injectable drugs. These drugs now operate using what is called just-in-time inventory. There is tremendous pressure for supply to meet demand perfectly. Drugs in this case are often expensive to produce, return a very low margin, and supply is extremely sensitive to problems with aging physical plants.

The government reimbursement system for these drugs drives the prices down, but at the consequence of a sensitive supply that has had more problems recently with shortages. I do understand the drug pricing theory and see how it can affect supply. What I am hoping is that in the future the committee will further explore specific outcomes.

I would like to have the generic manufacturers testify, like Bedford, APP, Hospira, or Teva. I would like to hear from Information Management Services, which tracks the drug data so precisely and produces the Drug Shortage Report that I referenced earlier. I would like to hear from GPOs or distributors. I would specifically like to ask what the impact of long-term fixed-price contracts is on supply. So for you witnesses, if any of you can answer this question or respond later in writing, I would be appreciative.

My question is, I understand the theory, as I just pointed out, how the pricing mechanism the government puts in place can affect supply. Can you give me one specific example of a drug that is on the current shortage list because of the pricing mechanism and

how that works? I would like to understand the real-world example in practice, not just in theory.

Dr. COBB. If you take the example of carboplatin, which is one of our chemotherapy drugs, when it came off patent and it came under the ASP model, the price of carboplatin plummeted by more than 60 percent.

So what happened was, you had several companies that would make the drug, but, as the pricing pressures came along, more and more manufacturers got out of making carboplatin. So it was the classic race to the bottom, so all you were left with was a few manufacturers that made the drug.

The problem then under the ASP model is that, once these competitors got out, the ones that were left behind did not have the ability to increase their prices again to make up for investments that they had to make in manufacturing because of the 6-month lag when ASP is reported. If they did that, then the price of the drug would become way over what cancer clinics like mine can pay. So the problem is that the manufacturers that are left cannot increase prices to make up for their costs.

Senator GRASSLEY. Anybody else want to add their experience or their point of view? Anybody? Or would you like to respond in writing?

Dr. THOMPSON. Well, I would just say, because my organization tracks drug shortages, you had mentioned a discussion with the pharmaceutical manufacturers and GPOs in the wholesaling industry, and it is a very important one to have.

Of the categories that shortages fall under, manufacturing is the biggest, quality issues is the other, and then "I do not know" is the other category. You have to believe within that category there are a lot of economic factors that exist. I just think that the pharmaceutical industry is going to have to describe what the real solutions will be that will help them in that category.

Senator GRASSLEY. All right. Go ahead if you had something.

Dr. GOTTLIEB. The example Dr. Cobb used I think is indicative of what has happened in this market generally, which is that the cost of goods has gone up and the prices cannot adjust to that. Some of these cancer drugs, including the one that he referenced, have precious metals in them, and we know what has happened to the precious metals market in terms of pricing. So, as the costs go up, you would hope in a functional market you could take a price increase.

But once these ASPs get blown, once they get busted and driven all the way down—sometimes by manufacturers that get in and out of the market but do not plan to be in there for any sustained period of time—you cannot raise the ASP again. It is sort of functionally impossible to bring the ASP back up, even if the cost of goods rises. So manufacturers, in turn, end up taking losses on these kinds of products as the cost of goods goes up.

Senator GRASSLEY. All right. Thank you all very much.

Thank you, Mr. Chairman.

Senator WYDEN. Thank you, Senator Grassley.

Senator Carper?

Senator CARPER. Good morning. How is it going so far? I have a question. Actually, two questions, if we have time. I would like

to start off with a question for you, Dr. Cobb, please. As you may know, Delaware is, and I think is considered by many, one of the leading States that are engaged in cancer research.

Delaware's cancer mortality rates when I was Governor were extraordinarily high, frighteningly high. We worked very hard those 8 years, and in the 10 years since, to bring them down. Now they are dropping faster, I believe, than just about any other State in the country. I think they are coming down at more than twice the national rate.

As much as we were alarmed by where we were 15 years ago, we are now very much encouraged. Recently the Helen F. Graham Cancer Center in Delaware was chosen to be, I think, one of the 16 sites in the National Cancer Institute's Community Cancer Center program. I am proud to say that the accrual rate of the patients into clinical trials in Delaware is 26 percent, more than 7 times higher than the national average.

Despite the strides that the researchers are making in my home State in cancer care, physicians have expressed the concern that drug shortages are hampering their clinical trials. They said that they are unable to enroll new patients into trials when drug supply is not assured, and they are concerned about compromising the results of the clinical trial when they have to substitute one drug during the trial.

I would just ask if you might describe for us the options that a doctor might have when overseeing a clinical trial where a necessary drug in the trial becomes in short supply, and what are the costs associated with this, and how might it set back cancer research if the trial is compromised or has to be restarted due to a drug shortage. Thank you.

Dr. COBB. First of all, Senator, Delaware should definitely be commended for its excellent track record of putting patients on clinical trials. That is an impressive improvement.

Clinical trials are really the only way we can improve the outcomes on cancer patients. We have seen over the last 2 decades a marked improvement in the outcomes for cancer patients, and it is really because of the clinical trial network that has been put in place by the National Cancer Institute, by pharmaceutical companies that are able to test new drugs against the previous standards.

When we do not have access to the generic drugs or the drugs that are in short supply, it makes it very difficult to do these types of trials. If you cannot do these types of trials, then progress in the war on cancer tends to grind to a halt.

Senator CARPER. As a practical matter, what happens when there is a shortage?

Dr. COBB. Well, when there is a shortage, if a patient is a good candidate for a clinical trial, oftentimes you cannot put them on because—let us say a patient is on a clinical trial that involves carboplatin, but I cannot get carboplatin.

Senator CARPER. Involves what?

Dr. COBB. Pardon?

Senator CARPER. Involves what?

Dr. COBB. Carboplatin, one of the chemotherapy drugs. If carboplatin is not available, then you look at this patient and say, well,

I cannot treat them on the clinical trial, so I have to give them something else, an ad hoc regimen. So that regimen may not be as effective. Plus, you have lost the opportunity to gain more information about how to treat cancer because they cannot enroll in a clinical trial.

Senator CARPER. All right. Thanks. Thanks for that response.

Dr. Thompson, if I could ask a question of you. You mentioned, I think, in your testimony that there are a number of factors that can play a role in causing drug shortages, and that the economic, scientific, and logistical factors leading to a drug shortage can vary among different sectors of the pharmaceutical industry.

We know that, in particular, quality issues and lack of manufacturing capacity are significant drivers in causing shortages, but that Medicare reimbursement rates, product discontinuations, and shortages of raw material may be contributing to the problem as well.

We heard about solutions ranging from increasing the reporting requirements on drug manufacturing to increasing reimbursement rates for certain drugs to creating tax incentives to increase production capacity. We all have talked about some of that here today.

When you consider the policy recommendations for addressing the complex nature of drug shortages, what solution do you view as the first priority, or do multiple solutions to address the various facets of this problem need to be implemented at pretty much the same time for us to be able to guarantee significant improvements in the availability of these drugs?

Dr. THOMPSON. That is a very good question. It is outside the jurisdiction of this committee, I know, but really the current legislation that is pending in Congress that would require notification to the FDA, confidential notification, so that they can help manufacturers resolve quality problems and help manufacturers that want to get into the business do that, would be a big help.

They have a track record of that: 101 times in the last 2 years they have been able to prevent a shortage from happening by helping a manufacturer fast-track an Abbreviated New Drug Application through the Office of Generic Drugs, or helping deal with a quality issue much quicker.

We think it is a parallel process that needs to occur. I think it is very important. Again, I have been working on this for a decade now. Economic incentives have not been discussed over that period of time. Those need to be discussed more thoroughly, and we do think that there are——

Senator CARPER. Really? So, in that entire decade, economic incentives have not been discussed?

Dr. THOMPSON. Sir, drug shortages have not gotten to this level of discussion over the time we have been working on them. There have always been drug shortages, but not the volume and type of shortages that exist now. So it is appropriate that more serious consideration is being given to these areas, but we think it is a parallel process. We do not have a lot of time to wait. We think the manufacturing issues, the regulatory issues that are in the current legislation, need to be addressed now, and that the economic factors need to be looked at at the same time very seriously.

Senator CARPER. All right. Does anybody else on the panel want to respond to that same question?

[No response.]

Senator CARPER. All right. Thanks very much. And thanks to all of you for being here and for your input.

Senator WYDEN. Just a couple of other questions for you all, to kind of dig a little deeper into the nuts and bolts of how some of the changes might affect people who are suffering today and are probably listening to the show, saying, what is Congress going to do to actually get some relief for my loved ones and my household?

One issue I wanted to ask you about, Dr. Thompson, because you have been looking at these issues, a whole host of issues and cost issues as well, is, do you have an idea of how much the shortages are costing the Federal Government in the form of reimbursement for costlier drugs? In other words, the kind of example that comes to mind is a brand-name drug that Medicare was paying for went generic. The generic drug is now on shortage, so I assume in some instances that the brand-name drug is being prescribed.

So, if that is the case, how many brand-name drugs are there like that, and, if you could give us some sense of the cost, that would be very helpful. Because I think one of the issues this committee will have to wrestle with is certainly we are going to look at ways to get more affordable generics, these injectables in particular, out to people who are suffering. But people are going to say, well, that is going to cost some money.

If Dr. Thompson can enlighten us on whether the government is now spending even more money on these costlier alternatives in terms of the shortage, that might be a way to make the case that, look, we can hold the costs down here by cutting the reimbursement for the costlier alternatives. So, do you have any sense of what the government is paying as a result of these shortages for brand names?

Dr. THOMPSON. We are just now beginning to drill down into our data to try to find some correlation to help answer that question. I think others may have a better answer than I do to this. But clearly, if there is a brand-name product available, that product costs more. Just the cost of——

Senator WYDEN. How many drugs? Can you give us a sense of how many drugs there might be? Would it be 5, would it be 10, would it be 20? How many drugs, even if you do not have an exact number, might fit this category of brand-name, being reimbursed, say, by Medicare when there is a shortage?

Dr. THOMPSON. Sir, I will probably have to get back to you on it.

Senator WYDEN. A significant number?

Dr. THOMPSON. I would say a significant number.

Senator WYDEN. So there is a possibility that this inability to fix the incentives may result in significant additional costs to taxpayers, to Medicare, for not dealing with the shortage?

Dr. THOMPSON. I think that is a plausible thing to say, yes.

Senator WYDEN. All right. Let me ask you all one other one. Maybe we just kind of go down the row. If you are listening to this, a loved one is suffering, you are waiting and hoping for treatment—and I have sort of reached the point, working on these

health care issues—I was director of the Gray Panthers for a lot of years, before I came to the Congress, working with senior citizens. People listen to these debates, and they want to know when there is going to really be a solution available.

Of course, just plucking a date out of the air is pretty hard to do, but let us take the kind of situation where, if the reimbursement issue was addressed in this committee, some combination of the policies that we are talking about here today—and as you know, Dr. Conti, I have some real questions about the relationship between physicians and the manufacturer, and you gave some thoughtful answers on that.

But let us say that the issue is resolved. How long would it take to get these drugs produced and out to patients? Senator Cardin was absolutely right. People consider this an urgent priority. They do not want to hear about how it is going to take eternity. So, as we wrap this hearing up, if this committee gets it right in terms of these reimbursement changes, how long would it take to get the drugs produced and out to patients?

Dr. CONTI. I think that is one of the key questions in this issue. Unfortunately, I think the time frame varies quite substantially by generic firm, and also by drug, in terms of responding to these type of incentives. I have seen estimates for getting production up and running anywhere between 4 months all the way to 7 years.

Senator WYDEN. So would it be fair to say again—I want to use the terminology that I used with Dr. Thompson, because my sense is that there are significant additional costs to the government for paying for costlier treatments because the shortage is not being dealt with. Would it be fair to say of you, Dr. Conti, that a significant number of the drugs that are in shortage could get out to people, say within 6 months? You said 4. Would that be a fair characterization?

Dr. CONTI. I do not know.

Senator WYDEN. All right. Do any of the others want to comment on a timetable? Because this is what people who are suffering want to hear, and that is why Senator Cardin asked the question. They want to follow these debates, but they want to see that sense of urgency. Do any of the others want to give us a sense of the timetable?

Dr. GOTTLIEB. Yes. I think the economic incentives and changing the pricing environment we talked about here today are important for getting new manufacturers into place and for expanding capacity to manufacture these drugs.

But it is not a short-term solution, in my view, in terms of the-next-6-months type of solution, because switching over an existing manufacturing line to make a new drug, you are probably looking at a year under optimistic situations. Standing up new manufacturing, you are looking at 2 to 7 years, and probably closer to 7 years, to stand up a brand-new facility de novo.

So that is a long-term solution to make sure that these markets do not get into trouble again in the future. I think shorter-term, we need to look at the existing capacity that has been taken offline. That is our best bet of trying to alleviate the shortage within the next 6 months. I do not think it is a sure bet that that is going to be a very efficient process, getting those facilities back online.

Senator WYDEN. They are not mutually exclusive. There can be efforts to deal with expanding capacity in the short term.

Dr. GOTTLIEB. Absolutely.

Senator WYDEN. But I continue to believe that people want to hear how long it is going to take to get at the root cause. We are wrapping this hearing up, and you all have been very, very helpful. For me, what it comes down to, Dr. Cobb, is what you said several hours ago when we began, that it is unacceptable to have you and wonderful practitioners on the front lines in this fight against cancer, like Dr. Druker, to have to say to patients every day in America, drugs that will relieve your suffering and relieve your pain, they are not available. We are not completely sure why, and they are having all kinds of debates in Washington, DC.

That is just not acceptable, so we have to find a way to speed this up. We have to find a way to speed this up in terms of both the short term that you just touched on a moment ago in terms of capacity, and then we have to shorten that kind of period for dealing with the root cause of the problem. This is not acceptable, in my view, to say to cancer patients, well, we will see what we can do in 7 years. That is just not right.

Would any of you like to have the last word, with the last word going to our witnesses?

[No response.]

Senator WYDEN. With that, you all have been very helpful. I think you are going to see significant bipartisan interest in this, and obviously this committee has jurisdiction over a key part of it. Led by Senator Hatch, we are going to get at it. Thank you all.

[Whereupon, at 11:40 a.m., the hearing was concluded.]

APPENDIX

ADDITIONAL MATERIAL SUBMITTED FOR THE RECORD

Hearing Statement of Senator Max Baucus (D-Mont.)
Regarding Drug Shortages
As prepared for delivery

The American inventor Charles Kettering once said, "A problem well stated is a problem half solved." We are here this morning to make sure we state the problem of drug shortages well, because doing so will help us find a solution.

In a recent study, nearly every hospital surveyed had experienced at least one drug shortage in the past six months. Nearly half of the hospitals experienced 21 or more shortages during that same time.

These shortages affect some of the sickest and most vulnerable Americans. As Dawn Grayson from Billings, Montana can tell you, when someone you love can't get the medicine they need, it can be terrifying.

This April, Dawn gave birth to a beautiful baby boy named Tanner. Tanner was born 11 weeks premature and developed a serious and sometimes fatal infection and had to have emergency surgery.

Because of his condition Tanner couldn't take a bottle like other babies. Instead he had to get all his nutrients, including calcium, through an I.V. mixture. But there was a national shortage on the type of calcium that Tanner needed.

Calcium is critical for muscle function and bone building, especially in young children, and he couldn't go without it. So, as is too often the case with shortages, the hospital had to give Tanner a substitute that caused complications.

In Tanner's case, the substitute caused chemical burns and permanent scarring on his arm and foot. Dawn is concerned it will affect Tanner's mobility as he gets older.

Dawn said, "My son has enough problems being premature, without adding chemical burns on top of an already difficult condition." She hopes that sharing her story will help us save other families from going through this same pain.

The number of patients like Tanner who are affected by drug shortages has grown over the past several years. More than half a million cancer patients were affected by drug shortages last year.

We have a responsibility to ensure that Medicare and Medicaid beneficiaries – and all Americans – have access to the care they need. We need to fix this problem to make sure this doesn't happen to more

patients like Tanner. Drug shortages deserve more attention, so I am glad Senator Hatch and I were able to schedule this hearing.

We are pleased to see that this issue is receiving greater attention. Specifically, Senators Hatch, Tester and Klobuchar have worked hard on this issue, and I commend them for their leadership.

Drug shortages are not a new problem. But the number of drugs and patients affected over the past several years has grown at an alarming rate. There were shortages on 211 drugs last year. That's up from 58 shortages in 2004.

The types of patients affected by a drug shortage show the seriousness of the problem. We read heartbreaking stories of drug shortages forcing cancer patients to forgo critical treatment. We hear stories about emergency room providers forced to use makeshift drugs when conventional drugs are in short supply. This compromises care in a place where even a minute's delay can mean the difference between life and death.

Each drug shortage has its own story. The causes vary; they include quality control issues, delays in manufacturing, disruptions in the supply of raw materials and changes in the prices of drugs.

The variety of reasons that cause drug shortages makes it difficult to find one silver bullet solution, but we can't tackle this problem without fully understanding the root causes.

Medicare and Medicaid pay for over $26 billion in prescription drugs each year. Both programs have a significant impact on the drug market. We look forward to hearing from our panelists where Medicare and Medicaid fit into this problem. We look forward to hearing how these programs can be a part of the solution. Are there things we can change? Will there be unintended consequences to these changes?

So as Mr. Kettering advised, let us work together today to state the problem well. Then let us find a solution. Let us help prevent cases like Tanner's from happening to others. Let us help patients like Tanner can get the care they need. And let us help moms like Dawn get the certainty they deserve.

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Testimony on:

Drug Shortages: Why They Happen and What They Mean

United States Senate

Committee on Finance

Patrick Cobb, MD

Frontier Cancer Center and Blood Institute

Billings, Montana

December 7, 2011

Chairman Baucus, Ranking member Hatch, and members of the Committee, thank you for giving me an opportunity this morning to talk to you regarding the impact of the drug shortage crisis on cancer patients throughout the United States.

I have been a private practice oncologist in Billings, Montana for more than 16 years. Every day patients come to my office asking a simple but critical question: "Can you help me?" For most of my career the answer has generally been "Yes." That is, until recently.

The current shortage of generic chemotherapy drugs has significantly limited our treatment options and, in many cases, have made treatments much more expensive. I want to share the stories of two patients to illustrate the problems we're facing.

Jerry is the father of two young children who came to the emergency room complaining that his nose wouldn't stop bleeding. The workup ultimately showed he had acute leukemia, a deadly disease but one that is very curable with chemotherapy. The standard treatment involves a generic drug called cytarabine, but that drug is in very short supply. We were able to find enough cytarabine to get Jerry through his first cycle of treatment. The problem is that now his condition demands a significantly higher dose of cytarabine, and we are not sure we will be able to find enough drug to complete treatment.

What do I tell Jerry, his wife, his parents, his kids? "Well, Jerry, with proper treatment you have a good chance of surviving this leukemia, but I don't know if we can find enough cytarabine. We might have to consider an alternative treatment, but one that doesn't have the same track record of cure." As you can imagine, this is not a conversation any physician should have to have with a cancer patient.

Another patient, Donna, a senior covered by Medicare, was recently diagnosed with colon cancer. She had surgery that removed the tumor, but the cancer had spread to three lymph nodes, putting her at increased risk that the cancer would return. By giving her chemotherapy post-operatively we decrease the chance of cancer recurrence and significantly improve the chances she'll be around to watch her granddaughter graduate from high school in three years.

Donna's chemotherapy regimen includes leucovorin, a generic drug that costs Medicare $35 and Donna's copayment is $9 for each treatment. Unfortunately, leucovorin is another drug in short supply. Because we can't find leucovorin, I have to use Fusilev, a brand-name drug. The problem is that Fusilev is significantly more expensive for Medicare and Donna — It costs Medicare over $24,000 more and Donna an extra $6,000 for the 12 cycles of treatment.

What do I tell Donna? "I'm sorry, but I have to substitute a drug that is going to cost you an extra $500 for each cycle of treatment, even though you won't get any better results."

I speak with oncologists from across the country on a regular basis and I can assure you that these patients' stories are not unique to Montana — this is a national crisis. Cancer treatment is being delayed, changed, and in cases even stopped on a regular basis.

When I'm faced with a cancer patient, I have to determine the origin of the disease before I can implement treatment. In analyzing the drug shortages, it is clear to me that the root cause is economics. It can be tracked back to the way Medicare Part B reimbursement was changed in the Medicare Modernization Act of 2003. Although I agree with the intent to better balance payments for cancer drugs and services, there have been unintended consequences.

The first consequence has been the closing of cancer clinics and the consolidation of clinics into the more expensive hospital setting due to Medicare reimbursement cuts to both drugs and services. In relation to drugs, you have to understand that the Medicare reimbursement system based on ASP, which is the average sales price of a drug, is price controlled. We have cases where the drug actually costs more than Medicare reimbursement.

The next consequence of the MMA is the drug shortage crisis due to a consolidating market of generic manufacturers. This is a result of a substantial drop in ASPs. At first blush, falling prices should look like a good thing for Medicare and patients. The problem is that there are now few manufacturers apparently willing to produce sterile injectable cancer drugs for what can be less than a dollar ASP per vial. Any manufacturing, regulatory, or quality problem is now magnified and leads to shortages when there are so few producers.

We have to treat the underlying cause of drug shortages, not just the symptoms. The drug shortage problem is a direct consequence of the reimbursement system that was set up by the MMA — it must be changed. It is critical that Congress move quickly to modify the Medicare reimbursement system, certainly not cut ASP reimbursement any further as some propose, and to create appropriate incentives for manufacturers. The lives of cancer patients hang in the balance.

Thank you for listening.

United States Senate Committee on Finance
Public Hearing
"Drug Shortages: Why They Happen and What They Mean"
December 7, 2011

Response to a Question Submitted for the Record for Patrick Cobb

Senator Olympia J. Snowe

Medicare Pricing

As many of you have observed, there is no silver bullet that will solve the issue of drug shortages. Yet there are some common themes and the majority of you have pointed to problems with Medicare pricing as one of the root causes of this multi-faceted problem. Some of you have also suggested tax credits for companies for developing new technologies in the production process, or other incentives to expand domestic capacity.

1. **Are there savings to be found elsewhere in the area of pharmaceuticals that could help offset the cost of addressing these pricing and reimbursement problems?**

   Not that I know of in this market. In terms of oncology providers, Medicare reimbursement for services and drugs have been cut so severely that there is massive consolidation taking place—facilities closing, especially in rural areas (as we have been forced to do), and mergers into large hospital systems.

AN ECONOMIC ASSESSMENT OF THE CAUSES AND POLICY IMPLICATIONS OF CURRENT SPECIALTY DRUG SHORTAGES

ORAL REMARKS

Rena M. Conti, Ph.D.
Assistant Professor of Health Policy and Economics
The University of Chicago

December 7, 2011

Chairman Baucus, Senator Hatch and members of Senate Finance Committee, it is my honor to speak to you today. I am an assistant professor of health policy and economics at the University of Chicago. My research work examines the regulation of the pharmaceutical industry.

SUMMARY

It is my contention that the defining features of the current drug shortage suggest that aspects of the supply of, the demand for, and the distribution of physician administered generic specialty drugs may constrain competitive market behavior. My evaluation of proposed policies suggests each proposal entails uncertainty regarding unintended consequences. The adoption of any one of these proposals would likely not substantially impact the availability of drugs in short supply currently nor in the future. Therefore, I suggest a combined approach.

INTRODUCTION

The use of drugs to treat disease is central to contemporary medical practice. Most drugs in short supply in the United States (US) treat cancer, are physician-administered and lost patent protection prior to 2000. Many have alternative therapeutic substitutes. The presence of shortages appears to be sustained over time and there is variation in the presence of drugs shortage by physician practice type and by geography.

CAUSES OF DRUG SHORTAGES

These features suggests there are four discrete aspects of the financing and organization of these drugs that have acted in concert to create the current crisis:

(1) Regarding supply, the international market for the supply of generic specialty drugs is highly competitive. These global firms derive profits from: reducing manufacturing costs and choosing drugs to produce that have the highest revenue potential. In the face of unanticipated changes in production costs, firms cannot increase their capacity to make these drugs quickly. We should expect firms to shift away from manufacturing older therapies with limited demand to other higher revenue producing drugs over time.

(2) Regarding demand, oncologists choose drugs to maximize the health of their patients. Adherence to current practice guidelines is a defining characteristic of the oncology profession. Therefore, physicians favor newer drugs with recently established safety and efficacy records.

(3) In addition, Medicare is the largest insurer of physician administered cancer drugs. Outpatient oncology practice revenues have been traditionally tied to the difference between insurer reimbursement for these drugs and their wholesale acquisition cost (WAC). Reimbursement to physicians for the administration of these drugs has declined over the past decade, putting pressure on oncologists' practice revenues. These changes reward the use of higher priced drugs that offer physicians higher "cost recovery".

(4) Regarding distribution, infused drugs are purchased by health care providers through purchasing organizations that negotiate price discounts from manufacturers. The amount of the discounted price and the preference for filling orders is not uniform across all members: rather it is based on a provider's purchase volume. It is likely that low volume, community oncology practices are the most vulnerable to interruptions in product supply.

AN EVALUATION OF REMEDIES

Numerous remedies have been proposed to ameliorate specialty drug shortages.

(1) Increase reimbursement to oncologists in the US to increase demand for drugs in short supply.

Proposals to increase physician payment include increasing the average sales price for selected products or switching the reimbursement for selected short supply drugs from average sales price to the wholesale acquisition cost.

Recent empirical work suggests physicians do appear to make prescribing decisions in part based upon variations and alterations in the reimbursement they receive from payers, holding patient benefit from a given therapy constant. Increased payment for certain drugs would also reduce the strength of the incentive for physicians to prescribe the drug with the highest cost recovery for their practice, in effect equalizing the incentives to prescribe generic and branded therapies for certain conditions. Manufacturers in turn could raise prices for these products to cover the additional expenses incurred in "meeting" demand.

An evaluation of the merits of this proposal include the following: (1) Would increased payment to physicians be "passed" through the manufacturers and if so, in whole or in part?; (2) Is WAC available for all generic drugs?; (3) Would the switch from ASP+6% to WAC for drugs in short supply generate enough revenue for manufacturers to compensate for the increased costs incurred to produce more drugs; (4) If an increased willingness and ability to pay for these drugs by providers generated a capacity building response by manufacturers, in what time frame would this response occur? I expect the time frame varies considerably by manufacturer and by drug; and (5) The strength of these reimbursement policies must be weighed against the importance of having oncologists adhere to currently available practice guidelines.

(2) Levy penalties on generic manufacturers to ensure the supply of selected medically necessary drugs.

It has been suggested that penalties on generic manufacturers via purchaser channel contracts could be strengthened and targeted to apply to the supply of drugs or drug classes that are "medically necessary" for the treatment of American patients. For generic drug manufacturers a penalty for producing certain drugs would act to increase their production costs.

Generic drug manufacturers' compliance with these potential penalties are predicted upon (1) the magnitude and timing of the penalty and the strength of it's enforcement; and (2) the ability of the manufacturer to offset these increased production costs through the command of higher prices from purchasers. Given the bargaining power of the industry, it is likely that manufacturers would be able to pass these costs off to purchasers. My examination of the generic manufacturers of oncology products in short supply suggests the majority of generic manufacturers produce multiple products across many therapeutic areas. These manufacturers are also multinational corporations. Consequently, it is possible generic manufacturers would be able to either absorb these additional costs into the price

setting of other generic drugs and/or pass these higher costs of production onto all domestic and international purchasers of a given drug in short supply.

RECOMMENDATIONS

My evaluation of these proposed policies suggest each proposal entails significant uncertainty regarding the intended and unintended consequences of their adoption. The adoption of any one of these proposals would likely not substantially impact the availability of current drugs in short supply for all physicians or alleviate the market conditions that may produce generic specialty drug shortages in the future. Rather, I believe effective public policy in this area should act to:

(1) Increase the reimbursement manufacturers receive for the production of drugs in short supply that are medically necessary and do not have therapeutic substitutes;
(2) Move toward equalizing the incentives specialist physicians have to prescribe equally effective branded and generic drug based treatments. These incentives could be financial or could take the form of other policies that encourage quantity enhancing, guideline adherent practice patterns and cost savings;
(3) Consider enacting penalties that work to compel generic manufacturers to invest in the capacity to produce an "adequate" supply of any medically necessary generic drug in case of domestic shortages or national emergency.

Thank you.

Statement before the Senate Finance Committee
On December 7, 2011

Drug Shortages: Why they happen and what they mean

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The views expressed in this testimony are those of the author alone and do not necessarily represent those of the American Enterprise Institute.

Introduction

Chairman Baucus and Ranking Member Hatch: I want to thank you for the opportunity to testify today before the Senate Finance Committee about the shortages of some critical sterile injectable and infused drugs that doctors and patients are grappling with. My testimony today expands on comments I gave last week before the House Committee on Oversight and Government Reform on these same matters. Among other things, today I want to get into more detail on the genesis of some of these challenges, and in particular, the role that I believe pricing policies have played in impacting the markets for these drugs. I also want to provide the committee with my perspective on the impact that these shortages have had on patients and on the clinical practice of medicine. Finally, I will relate some new proposals for mitigating these challenges that I hope this committee will consider.

The problems have affected mostly older infused or "parenteral" drugs that are sold as generic medicines. Because these drugs have lost patent protection, they are typically sold at low prices and for slim profit margins. In fact, of the drugs that are in shortage, there is a clear correlation between price and availability – with many of the cheapest infused medicines also being the ones that seem most likely to be in shortage. These drugs are often sold for very low prices, sometimes just several dollars for a single dosage vial of a medicine. As a result, the cost of manufacturing ends up comprising a sizable proportion of the overall price of the finished medicine. In some cases, these drugs are being sold at a loss to their manufacturers once all the production and distribution expenses get fully loaded into the cost. The economic problems are widespread, and deeply embedded in the markets for these drugs. As a result, I fear the shortages will get worse before we see some relief.

Other countries are also experiencing drug shortages.[i] Since many of the parenteral drugs manufactured for the U.S. are also sold in Canada, some of the same drugs in shortage here are also in shortage North of our border.[ii] [iii] Yet in the U.S. the critical medicines that are in scarce supply, and the protracted nature of the underlying causes of these shortages, make our situation uniquely challenging. In Europe, where generic medicines are often sold at higher prices, and where regulation of manufacturing has been more even in recent years, countries are facing few of the same shortage problems that we are seeing in the U.S.

I want to start today by reviewing the current problems, and providing the committee with some measure of the impact that these shortages are having on patient care. I will then review what I believe are some of the policy problems that have contributed to these current woes, and follow that with a description of what I believe are some potential solutions.

I should note up front, that I do not believe there is a discrete set of policy problems that have created these shortages. Nor do I believe there is a single collection of measures that can mitigate these circumstances. In fact, it is this absence of an identifiable set of primary causes that makes this problem so hard to resolve. Rather, the reasons for these shortages are multifactorial. Moreover, where policy failings have played a role, their impact has unfolded over many years and over successive political administrations. These elements are part of the reason why these problems are so protracted, and so hard for us to resolve.

Notwithstanding these complexities, I believe the best place for policymakers to begin addressing these challenges are with the common policy problems that are threaded, to

varying degrees, through many of these shortage episodes. They provide the most logical place for policymakers to start addressing the root causes of these drug shortages.

Measure of the Problem

Today, about 200 sterile injectable drugs are on the current shortage list kept by the American Society of Health-System Pharmacists.[iv] [v] The vast majority of these shortage drugs (more than 80%) are generic medicines. Of the total market for generic sterile injectable drugs, fully 50% of these medicines are currently on the shortage list.

It has been said that the problems are being fueled by shortages of raw materials. Also, firms are said to be discontinuing manufacture of older generic drugs in favor of newer and more profitable ones. These elements, while at play in some of the individual drug shortages, tell only a small part of the story. The fact is that total generic manufacturing capacity has increased in recent years (from 54 million unites to 56 million units over the last five years).[vi]

The more revealing market phenomenon is the growing concentration of manufacturing in a smaller number of increasingly large suppliers. This consolidation creates a lot of operational efficiency. That enables these low-margin products to be produced at their low price points. But it also creates some additional risks. It means that when any single manufacturer experiences a disruption in their production, a significant shortfall can ensue across a whole multitude of different drugs. It should therefore be no surprise that only one or a few companies manufacture many of the drugs on the shortage list. Of the 168 products that IMS Health lists on its shortage list, seven currently have no suppliers, while 56 products have one supplier, and another 23 have two suppliers. Moreover, the manufacturing of most of these generic sterile injectable drugs is concentrated about six very large suppliers.[vii]

Oncology drugs make up the highest share of the drugs in shortage, fully 16%. This impacts nearly 550,000 patients annually, comprising 28 different generic injectable cancer products).[viii] Shortages of drugs have triggered clinical mistakes and bad outcomes in situations where patients received medicines that prescribers weren't accustomed to using.[ix] The medical literature is replete with case reports of critical, life-saving drugs that have been in shortage, where doctors were forced to adopt suboptimal alternatives. For example:

Since autumn 2009 the anesthetic drug propofol has been facing production issues.[x] Some institutions lacking propofol have used midazolam or dexmedetomidine instead. Both agents are similar to propofol but do not precisely mirror the quick time to onset and offset or level of sedation provided by propofol. In each case, there are reports of patients becoming dangerously over sedated because hospital staff was unfamiliar with using the new agents.[xi]

In the case of propofol, the FDA allowed another version of the drug to be imported temporarily.[xii] However, this alternative medication does not contain an antimicrobial retardant. As such, strict aseptic technique had to be used in administering this version of the drug --- techniques clinicians weren't accustomed to requiring with the drug.[xiii]

Severe shortages of leucovorin, used to treat colorectal cancer, prompted the American Society of Clinical Oncology (ASCO) to issue a clinical alert in 2009. ASCO suggested substitution of leucovorin with levofolinate, which is much more expensive and is only

approved by the FDA for use as a rescue drug after administration of high-dose methotrexate in patients with osteosarcoma. Levofolinate in combination with irinotecan and fluorouracil seems effective in patients with metastatic colorectal cancer, but it is unclear whether addition of this agent to other chemotherapy regimens would replicate the responses expected of leucovorin; thus there is a risk attached to this strategy.[xiv]

I have seen some of these problems first hand. I practice hospital-based medicine. When a drug is declared to be in shortage, there is pressure put on doctors to find alternative therapies, in order to conserve the shortage drugs for the most urgent cases. I have never seen a situation in my own clinical work where doctors couldn't find an adequate alternative drug to substitute for a medicine that was not available. But I can tell you that I have seen the process of grappling with these issues cause problematic delays in administering critical care. Many hospitals are being forced to ration key medicines and patients to sit on waiting lists for vital drugs.[xv] For all of these reasons, the drug shortages are also costing a lot of money, adding to an already overburdened healthcare system. The costs associated with managing shortages in the United States are an estimated to total $216 million annually.[xvi xvii]

Finding Solutions

In our search for the cause of the shortages, and the pursuit of solutions, we need to be careful not to confuse the consequences of the problems for its root causes.

The causes of these shortages are often multifactor and stem from many conditions outside of the easy grasp of policymakers. I would urge this committee to focus its attention on those elements that are in its direct purview and that re-appear as common factors that are woven through many of these shortage episodes. To these ends, there are things we can do immediately to help mitigate some of the pressure on the market for these drugs. There are steps we need to take that may not have an immediate impact, but will start to repair these markets for the long run. I group these elements into three categories:

The first are mechanisms that make prices sticky, limiting profitability and precluding investment in new supply and more efficient manufacturing.[xviii] The policies that make prices inflexible also prevent firms from taking price increases as their cost of goods rise.

The second are regulatory challenges that have made production of these drugs safer and more reliable, but also in some cases substantially increased the cost of goods at the very time that policies have made it hard for producers to take and sustain price increases.

The third category is market structures that prevent firms from being able to earn appropriate returns when they invest in key improvements in manufacturing that creates production that is more reliable and can be more easily scaled to meet changes in demand.

Regulation of Drug Pricing

The most significant issue in these markets is that pricing is sticky. When demand for these drugs increases, or more importantly, when the cost of developing these medicines rises, manufacturers can't take and sustain price increases to make up for these market changes.

This makes it hard for manufacturers to make the long-term (2-7 year) investments needed to stand up new facilities or upgrade existing facilities to produce more supply.

A search for the origin of that sticky pricing has to begin with the way Medicare reimburses these products. A 2003 law sets the price Medicare will pay for physician-administered drugs to an "average sales price" that is at least six months old at any given time because the average is computed off six months of backward looking prices. This flawed concept means even if a generic firm raises its price to reflect increased production costs, Medicare won't immediately pay the new price until about six months later. As a result, the purchasers of a drug (in this case, mostly hospital outpatient clinics and individual physicians) lose money on these drugs for months at a time since the price they pay for the drug could be significantly higher than the lower "average sales price" that Medicare reimburses for the medicine.

This makes it hard for manufacturers to take, and sustain price increases to reflect demand or – more importantly -- their rising cost of producing these goods. For one thing, even if a single manufacturer raises its price, this price increase will be diluted once it gets averaged into the prices charged by competitors. Unless manufacturers were to illegally collude to raise their prices simultaneously, the average sales price will always be pushed lower by the impact of the lowest cost product. This might be a firm who can produce drugs at lower costs only owing to uneven regulation of manufacturing facilities that raises costs for only a handful of firms at a time. Or it might be firms who are willing to take losses on particular generic drugs in order to win more lucrative contracts on other medicines. Once the ASP gets driven down by a single producer, who might get into the market for only a very short time, it is very hard for the ASP to ever rise again after it has been pushed to the floor.

Moreover, many of the manufacturers producing these parenteral generic drugs do so in order to win group purchasing contracts with large institutions. They often view these drugs as "loss leaders" that allow them to get contracts that enable them to sell more profitable medicines. For this reason, they're reluctant to raise prices to match rising production costs if it means putting at risk much larger contracts covering dozens if not hundreds of other products. But that also means they will be reluctant to invest in improved manufacturing capacity. When faced with rising production costs, the easier path for some manufacturers is to cease production of a drug entirely rather than raise prices and disrupt contracts.[xix]

In order to make the long-term, capital intensive investments needed to bring on new manufacturing capacity, generic firms would need to know that they can take, and sustain, price increases over a reasonable period of time. It should come as no surprise that a recent analysis by the Department of Health and Human Services found that among the group of drugs that eventually experience a shortage, average prices decreased in every year leading up to the shortage. The mean price decrease over these periods leading up to the shortages averaged of as much as 27%. By comparison, the average prices of drugs never in shortage over this period, in most cases, rose.[xx] Moreover, any examination of the list of shortage drugs will show that the lowest-priced drugs are also the ones most often in shortage.

The bigger issue with the way Medicare reimburses these drugs, however, is the way it sets a single, flat price for each category of medicine rather than paying for these drugs individually. Medicare assigns a single "billing code" to each category of medicines. The agency then establishes a single rate (computed off the average sales price) that it will pay for

each code, and in turn, each drug category. This means that the price reflects the blended average of all the drugs in a particular category, regardless of which manufacturer is producing the drug. So even if a drug has multiple manufacturers, some better or higher-cost producers than others, all of the drugs in a particular category will be paid the same rate.

Since FDA's enforcement of facilities is often uneven, at any given time one particular manufacturer might be facing more scrutiny, and in turn higher production costs, relative to its competitors. By lumping all of the drugs into the same billing code, the price paid ends up reflecting the terms of the lowest cost producer. This situation creates pressure to shave down manufacturing costs. Once ASP falls to a new, lower level, it is hard for it to rise again because of its stickiness. So firms end up in a race to the bottom on manufacturing costs.

This race to the bottom on manufacturing can work reasonably well in producing significant savings when it comes to products that are easy and cheap to manufacture, like small molecule drugs (pill forms). But it creates significant risks in markets like sterile injectable drugs, where the manufacturing is not a trivial affair and a constant drive to lower costs can mean necessary manufacturing investments are forgone. The end result is that there is little margin left over for investing in expanding or improving manufacturing facilities.

Regulation of Drug Manufacturing

The regulation of pricing is made more problematic by the fact that production costs have been increasing owing to more stringent regulation of manufacturing. In recent years, the Food and Drug Administration (FDA) has gotten tougher on potentially dangerous problems that have long plagued the production of some injectable generic drugs. These include problems with sterility, and particulate matter getting into the solutions.[xxi]

The FDA has real concerns about the integrity of how some of these drugs are manufactured. For example, contribution to the finished solution from equipment, process, components, and packaging should never be considered acceptable. But the fact is that there has been a fairly rapid tightening of the regulatory scrutiny of these products over a short period of time. To the degree that the market for these products was already populated with some less well-capitalized manufacturers; that increased regulation has caught them off guard. Low margin producers can't easily meet new regulatory mandates.[xxii]

The regulatory scrutiny isn't the cause of shortages, but another of the multiple factors that have contributed to the conditions challenging these drug makers.[xxiii] With its vigilance heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. As a result, in 2010, product quality issues -- and the subsequent regulatory actions taken by FDA to address these problems – were involved in 42% of the reported drug shortages.[xxiv]

The increased FDA scrutiny doesn't just apply to the finished forms of these drugs, but in particular, to the ingredients in these medicines – the Active Pharmaceutical Ingredients or API. After the safety issues related to Heparin several years ago, FDA dramatically stepped up its oversight of API suppliers, especially ingredients coming from foreign sources.

There are other factors that have contributed to a sharp and rapid increase in the cost of goods of many of drugs. For example, precious metals such as platinum are a component of some drugs. It's clear what have happened to commodity prices in recent years. But changing regulatory standards are the most significant driver of rising cost of goods in this space. If we want to maintain high standards, we need policy measures that accommodate the economic impacts. This begins with making sure the regulations governing drug manufacturing, FDA's Good Manufacturing Practices (GMPs), are as efficient as possible. When it comes to injectable drugs, this starts with the process for remediating facilities recently taken off line as a result of regulatory action. FDA must prioritize getting these facilities producing as quickly as possible after necessary renovations are made.

To these ends, an issue at play in these shortages relates to the backlog that FDA currently has for generic drug manufacturing supplements. The FDA expedites the review of supplements related to shortage drugs, so the backlog doesn't directly affect these products. But the agency's expedited review often kicks in only once drugs approach shortage status.

For the rest of the almost 3,000 supplements that are on backlog, these applications can sit for months and sometimes years owing to a lack of resources to enable their timely review. It seems almost inevitable that some of these backlogged manufacturing supplements sat in this backlog while the drug approached the precipice of the shortage list.

The backlog in reviewing manufacturing supplements can add as much as a several year delay to approval of those manufacturing changes. These supplements are usually requests to expand or modernize manufacturing facilities. The delay in reviewing these supplements can have significant economic implications. For example, to submit these applications, companies may also have to manufacture three commercial batches with the new manufacturing process while still running the old manufacturing and only selling the old batches. The backlogs are now so long the new batches may become worthless by the time the new manufacturing facility is approved. The financial burden to the generic drug manufacturers of having to waste these first-run batches is a huge disincentive to modernize.

FDA's position has been that without additional resources, they cannot hire a sufficient number of chemist-reviewers to solve the problem. To these ends, the Generic Drug User Fee program should provide FDA with money to tackle this backlog.[xxv] Congress should build into this legislation specific measures to allow FDA to prioritize resources to the review of supplements related to the manufacture of generic sterile injectable drugs -- not only those drugs that are currently in shortage but all of the generic parenteral drugs. That way we will not only tackle current shortages but also better avoid future ones.

Proposals for Reform

To fix the problems with inadequate supply for generic sterile injectables, we should lift existing price controls when it comes to critical injectable drugs that are generic, and take steps to provide manufacturers with incentives for making improvements in the manufacture of these drugs that can lead to a more stable supply and more scalable production facilities.

First, Medicare should move away from the flawed "average sales price" when it comes to reimbursing the generic sterile injectable drugs and pay for these drugs according to a more

flexible, market based price that could more easily adjust to market conditions. One consideration is to reimburse these drugs based on the price paid by wholesalers on the open market. This wholesale acquisition cost (WAC) is already collected and reported to Medicare. Reimbursing the parenteral drugs according to WAC would allow generic firms to adjust charges to match rising production costs and demand. Congress might also consider allowing ASP to be "re-set" in some fashion for drugs that are approaching the zone of shortage, or are considered critical and prone to shortage by some authoritative group such as USP, FDA, or the Society of Health System Pharmacists. This re-setting of ASP could be to a more market-based price – either WAC (which has its own flaws) or some new "spot" price that Medicare requires reporting on that is more forward looking.

These drugs should also be exempt from Medicaid price-control schemes that serve to distort market prices and reduce profitability and incentives to invest in new production. These include Medicaid Best Price rules and the 340B drug discount program. With respect to 340B, perhaps the most damaging proposal would be to expand this program to the hospital inpatient side. Such a proposal could have a significant impact on profits on these drugs, and could dramatically impact decisions to invest in new lines or expanded facilities.

Medicare can also allow these drugs to have individual billing codes, rather than paying for each class of drug according to the same billing code. This would allow manufactures to price their drugs individually. It would help to eliminate the race to the bottom on pricing and, in turn, cost of goods. If manufacturers made legitimate improvements in their manufacturing to enable more stable supply, they could try to represent these improvements in contracting discussions to secure better pricing. Some purchasers might well be willing to pay for supply that's produced from more up-to-date and reliable facilities. Providers are becoming increasingly conscious of how and where drugs are manufactured. Allowing drugs to have individual codes would let manufacturers price products to reflect these attributes.

We should consider policy constructs that would give manufacturers a financial incentive to develop intellectual property that improved the manufacturing characteristics of generic medicines even if these changes it didn't alter the clinical properties of a drug. FDA could be directed to establish criteria for which manufacturing improvements are believed to allow for more reliable, stable, and scalable supply. In turn, manufacturers can be permitted to make limited claims in labeling attesting to upgrades that meet these manufacturing criteria.

A significant factor in recent shortages is the lack of excess capacity in the market owing to economic factors (the profit margins on these drugs are so slim it doesn't make economic sense to keep excess manufacturing capacity on hand). The manufacturing capacity that exists is not scalable, meaning that production cannot be easily ramped up at one manufacturing site to make up for shortfalls should another production site experience problems. If only a few companies make a drug and one of them encounters a manufacturing problem, the remaining competitors may not be able to meet the demand.[xxvi]

To address these challenges, once producers invested new processes and are approved to make certain claims on their labels that reflect improvements in manufacturing to make the process more reliable, these claims could then trigger specific incentives – perhaps guaranteed purchase by government programs or preferential pricing under Medicare (for example, through a pass through payment under the DRG). This would provide a direct

incentive for investing in the kind of manufacturing improvements that can help ensure a more scalable, and less trouble-prone supple of a product.

We need to view production capacity for critical drugs as a national strategic asset. In the past, government approached similar issues by coming up with targeted incentives (such as tax credits) to encourage development of more domestic manufacturing capacity. This was the approach taken to enabling more domestic capacity for production of flu vaccine. That episode provides some good proxies for how we might resolve the current shortages.

Having more investment in domestic manufacturing will also help stimulate creation of skilled domestic jobs. Right now, there are very few companies investing in new domestic facilities because of the economic advantage of taking these activities overseas.

When a system of competitive bidding drove down the price of flu vaccine to a level that made investment in expanded and improved manufacturing unviable, some severe shortages arose when outdated manufacturing facilities experienced regulatory problems. The situation was resolved with policies that, among other things, created incentives for development of new, domestic manufacturing capacity; and regulatory approaches that made evaluation and approval of new manufacturing sites and brands of vaccines more efficient.[xxvii]

In the market for generic injectable drugs, a large part of the reason why adequate incentives don't already exist for investment in new production capacity relates to the inability of manufacturers to take and sustain price increases to offset the cost of these investments. So first and foremost, we need to fix these pricing policies. Many stem from the way Medicare treats these products. But we shouldn't expect these solutions to have an immediate payoff.

In the short run, there may be little we can to stimulate investments in new production capacity that will translate into immediate supply increases. The bottom line is we need to address policy reforms that will enable us to have more stable supply in the future, but it will take time (in some cases years) to stand up these new facilities. To resolve these shortages in the short term, we should focus equal attention on the existing manufacturing capacity that is available, but has been taken offline as a result of regulatory findings. A significant amount of manufacturing capacity is currently undergoing remediation owing to concerns raised by the FDA. The most immediate impact we can have on these shortages is to make sure the process for getting this manufacturing capacity remediated, and bringing it into regulatory compliance, is as efficient as possible. We should focus some attention on the resources that would enable FDA to help producers get these renovated facilities quickly back on line.

Conclusion

The problems fueling the recent shortages of sterile injectable drugs do not lend themselves to easy solutions because these episodes aren't typically driven by a single, common cause. Each shortage has unique features. In addition to the factors cited in this testimony, byzantine contracting arrangements (where large GPOs lock in prices for a few years at a time, and put caps that prevent manufacturers from taking price increases), inefficient sourcing arrangements, a reluctance of hospitals to buy products 'off contract,"[xxviii] problems with the sourcing of raw materials,[xxix] and a myriad of other factors all play a factor.

There are, however, some flawed policy threads woven through these episodes. To the degree that some of these common issues stem from the way the price and manufacture of these drugs is regulated by government agencies, this presents policy makers obvious levers to start repairing this market. Before we start manipulating factors not in the control of government agencies, we should address factors that in the direct purview of this committee.

I know one of the proposals before this committee is a system for early notification to FDA of impending shortages.[xxx] I don't believe that relying on early notification of impending shortages is going to resolve these problems. In fact, I fear such a policy construct could make matters worse, by institutionalizing these shortages. Current proposals call for early notification from pharmaceutical companies when a factor arises that may result in a shortage. These factors may include changes made to raw material supplies, adjustments to manufacturer production capabilities and certain business decisions such as mergers, withdrawals or changes in output. In the end, the net effect of this legislation may simply be to provide an additional disincentive to firms who want to take one of these actions, even though these may be precisely the steps necessary to help ensure better long term supply. Companies will be reluctant to take business decisions that invite FDA inspectors to pick through their facilities and operations, even if these decisions might shore up shortage drugs.

If the Senate does grant FDA with this new authority, I would urge members to monitor its implementation closely. To the degree that FDA would get information from manufacturers that could help to predict shortages, we should audit this process. If shortages continue to occur, we should understand why these were allowed to take place in situations where FDA had warning of the impending problem. In some cases, there will have been regulatory steps that could have been taken to mitigate a future shortage. We should understand whether the consequences of the shortage itself were less significant than the consequences of whatever regulatory steps might have prevented the shortage situation (such as allowing a facility with deficiencies to nonetheless continue to produce and ship drug under closer supervision).

Congress should also take steps to make sure FDA's internal communication around these issues is efficient and properly resourced as well. I was told of at least one situation where a major manufacturing facility was voluntarily shut down and created a shortage of some critical drugs, but FDA's drug shortage office was not aware of the situation until after the fact even though FDA's field inspectors knew about the pending action for some time.

Some also blame these shortages on what they refer to as "manipulation" of drug middlemen or so-called "gray market" distributors. However unpleasant, the markups charged by small distributors often reflect their higher costs, and aren't simply profiteering as has been alleged. In select cases where middle market distributors are using the existence of a shortage to earn windfall profits,[xxxi] and can be legitimately said to be taking advantage of these situations, the activity – however unsavory – is also not a cause of the shortage, but a sad symptom of the larger problems. [xxxii] We need to make sure that in our effort to come up with proactive measures to address these shortages, we don't end up making them worse. Cracking down on inappropriate profiteering, while an important endeavor, won't solve the shortages and will only add to our challenges if it ends up also impacting the legitimate activity of small distributors that help plug gaps in the existing supply chain. Legislation to address the "gray market" needs to make clear distinctions between legitimate and illegitimate activity, and it may be hard in some cases to distinguish this on price alone.

Many small distributors routinely provide critical-need products to hospitals that cannot otherwise secure these same products from their primary wholesalers. This is especially important in rural areas. Moreover, small and independent distributors typically must purchase products at prices above the Wholesale Acquisition Costs. They cannot access drugs at the lower prices that GPOs negotiate with manufacturers. As a result, the difference between the higher prices charged by small distributors and those typically provided to hospitals by GPOs can often be misleading. What might appear as an enormously priced drug being offered by a small distributor may actually reflect an appropriate mark-up.

Like the "gray market," the lack of qualified manufacturers for these drugs is also not a cause for the shortages.[xxxiii] Here again, the lack of qualified manufacturers is another symptom of the underlying problems. True, the absence of multiple manufacturers makes shortages for any particular drug more likely to occur. But branded drugs typically have only a single manufacturer, and aren't facing the same production problems. Under the right circumstances, a handful of adept companies can supply these markets. The existence of shortages in the market for sterile injectable drugs has more to do with the lack of pricing power in this market, and the under-investment in manufacturing in an enterprise where the margin for error is narrow, and driving down cost of goods creates its own risks.

Policy makers have also suggested that one way to alleviate the U.S. shortages is to import drugs manufactured for other markets. Rather, I believe the question we should be asking is why the companies making these drugs aren't choosing, on their own volition, to market these drugs inside the U.S. in the first place. Pricing is certainly one factor. Companies can often charge more for the generic parenteral drugs when they sell these medicines in Europe. But regulation is also a factor. In some cases, the newer facilities that these drugs are being manufactured in haven't met FDA clearance. Bringing our regulatory standards up to date, making it easier for manufacturers to adapt plants with new technologies, and harmonizing GMP requirements across different established markets like Europe would better enable manufacturers to enter the U.S. with reliable supplies. All of these elements should continue to be part of FDA's efforts to modernize its approach to GMPs and address the shortages.

The only way to improve the availability of these products is to make it possible for firms to keep pace with rising production costs and earn enough returns to invest back in better manufacturing that enables stable, safe, and more scalable supply. Policies enacted over the last few decades have systematically eroded the ability of manufacturers to price these products in ways that keep up with rising costs. Instead, this market has been challenged by a race to the bottom on manufacturing costs. This isn't a healthy dynamic in markets where production is not a trivial affair and where increasing regulatory requirements demand new investments in manufacturing facilities. We need to reform the policies governing how these products are priced if we're going to attract new investment into these important areas.

# # #

This testimony is based on written testimony delivered before a hearing of the House Committee on Oversight and Government Reform, Healthcare Subcommittee on November 30, 2011. Dr. Gottlieb consults with and invests in healthcare companies.

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[xix] Scott Gottlieb. Solving the growing drug shortages. The Wall Street Journal, November 07, 2011. A21 available at http://www.aei.org/article/health/healthcare-reform/solving-the-growing-drug-shortages/

[xx] ASPE Issue Brief, "Economic Analysis of the Causes of Drug Shortages," October 2011. For the 44 sterile injectable oncology drugs in shortage since 2008, these drugs experienced an average price decline of 26.5% between 2006 and 2008; 6.3% between 2008 and 2011; and 27.4% between 2006 and 2011. By contrast, the 28 generic injectable oncology products not in shortage since 2008 experienced small price increases over all these time periods.

[xxi] Data presented by Steven Lynn, Chief, Recalls and Shortages, FDA/CDER Office of Compliance, Division of Manufacturing and Product Quality. Recalls, presentation to CASA, May 20, 2011, Baltimore, MD.

[xxii] Corresponding to this increased regulatory scrutiny, the number of shortages has also increased almost proportionally. In 2005 and 2006 about 25 sterile injectable drugs were said to be in shortage by FDA. By 2009 that number had increased to about 75, matching the rise in the number of enforcement actions FDA took. By 2010 the number of parenteral drug shortages was put at more than 125 by FDA.

[xxiii] To Precent Drug Shortages, Don't Look to Inspections, FDA Says. The Pink Sheet Daily, August 22, 2011

[xxiv] The ASPE report finds that problems in manufacturing are linked to 54% of shortages of sterile injectable drugs. The report finds that some of the largest manufacturers of sterile injectable drugs have had serious quality problems leading to temporary voluntary closure or renovations of major production facilities. This means that quality problems that affect an entire plant may result in shortages for many drugs.

[xxv] Congress has set the floor for FDA's Office of Generic Drugs funding at $52.947 million in fiscal 2012, almost 5% less than the minimum of $55.5 million it directed FDA to spend on OGD in fiscal 2011. FDA proposed a budget of $88.8 million for OGD in fiscal 2012. But $40 million of that was to have come from $40 million in generic drug user fees that are not yet authorized.

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[xxviii] Wynn Bailey. Globalization of the Life Sciences Supply Chain. Contract Pharma, January/February 2011. (available at www.contractpharma.com)

[xxix] More than 80% of the raw materials used in pharmaceuticals come from outside the United States.

[xxx] Preserving Access to Life-Saving Medications Act (S.296)

[xxxi] Mandy L. Gatesman and Thomas J. Smith. The Shortage of Essential Chemotherapy Drugs in the United States. New England Journal of Medicine 2011;365;18

[xxxii] The report from ASPE states: "These gray market distributions appear to be a result of a drug shortage, not a cause, but the potential for hoarding and strategic behavior in the gray market is a concern with respect to future policy actions."

[xxxiii] According to the ASPE analysis, most of the production of a given drug is by three or fewer manufacturers in this space. Analysis of a sample of 33 generic sterile injectable oncology drugs shows that of 33 drugs, for 28 at least 90 percent of total unit sales in 20910 was by 3 or fewer manufacturers.

STATEMENT OF HON. ORRIN G. HATCH, RANKING MEMBER U.S. SENATE COMMITTEE ON FINANCE HEARING OF DECEMBER 7, 2011 DRUG SHORTAGES: WHY THEY HAPPEN AND WHAT THEY MEAN

WASHINGTON – U.S. Senator Orrin Hatch (R-Utah), Ranking Member of the Senate Finance Committee, delivered the following opening statement at a committee hearing examining the impact of drug shortages in America:

Chairman Baucus, thank you for convening today's hearing on such an important issue affecting our nation's patients and caregivers. We have all seen the disturbing stories in the press over the past several months about doctors unable to access critical medical products for their patients, and the impact that these drug shortages have had on patient care. While there is no doubt that increased attention and coordination has occurred between manufacturers and the government to begin addressing this problem, clearly more can be done to mitigate these shortages in the future.

Drug supply shortages are not new. Any product that involves complex manufacturing and distribution could face some supply challenges. What is new is the volume of shortages, the importance of the therapies that are experiencing shortages, and the challenges these shortages present to patients and caregivers. Every year since 2005, drug shortages have become more prevalent and widespread. In 2009, there were 157 products on the FDA's shortage list, and in 2010 that number increased to 178. According to the University of Utah, which keeps track of shortages for the American Society of Health System Pharmacists, the total number of drugs in shortage currently exceeds 275 FDA- approved therapies and continues to grow.

What is the impact of these increasing shortages? This crisis means worse outcomes for our patients, increased costs for caregivers and the government, slower medical advancement, and a persistent undermining of confidence in our country's healthcare system. Many of these drugs in shortage are used in current oncology treatment regimens. Not only are drug shortages impacting current treatments, they are harming future patients by delaying clinical trial results, increasing the length of clinical trials, and raising costs for research organizations.

Our federal payer system is also bearing the cost of drug shortages. Clinicians are forced to scramble to find alternative treatment options for vulnerable patients, often at a much higher price for both the patient and the government. According to research by Premier, drug shortages could cost U.S. hospitals at least $415 million annually. This is because more expensive substitutes are often needed, intermediaries significantly mark up the price of these drugs, and there are additional labor costs associated with finding these alternative solutions.

So what is causing this crisis? While this is clearly a complex issue, I believe we must look at the impact of federal programs on the generic injectable market. Seventy-four percent of drug shortages involved sterile injectables in 2010. I do not believe it is simply a coincidence that shortages are disproportionately impacting products with highly complex manufacturing

processes that are also some of the lowest priced therapies. And I am not the only one to think that economic incentives play an important role in this issue. As recently highlighted in an article in the *New England Journal of Medicine*, experts contend that federal government pricing and rebate programs are a significant contributing factor to the current drug shortage crisis. The article also notes that there is an "untapped capacity" to produce generics but indicates that incentives to attract new entrants would be required to create redundancy in the market.

Mr. Chairman I ask unanimous consent that this article be included in the record.

Current pricing structures have been very effective at driving generic utilization. However, they may not fully capture or reward the costs associated with the complex development and manufacturing of injectables, as opposed to the more straightforward manufacturing process in the pill market.

The current situation is simply unacceptable, and we must act to address this growing crisis. As most of my colleagues know, I am working on a solution that will continue to improve coordination between manufacturers and the government, but that also addresses some of the federal price control and rebate structures that prevent the true costs of bringing these important medicines to patients from being adequately addressed.

I urge my colleagues to join me in working to solve this problem in the very near future. Senator Baucus, thank you again for convening this hearing today. I look forward to hearing from our witnesses and having a serious discussion about the steps we must take to address this crisis.

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SUBMITTED BY SENATOR HATCH

From **The New England Journal of Medicine**

October 31, 2011

Drug Shortages—A Critical Challenge for the Generic-Drug Market

By Bruce A. Chabner, M.D.

While the oncology community has been focusing much of its attention on the remarkable activity and enviable science related to the discovery of targeted drugs, the importance of standard cytotoxic therapeutics has suddenly become apparent, owing to shortages of the common workhorses of cancer treatment—methotrexate, leucovorin, 5-fluorouracil, cytosine arabinoside, vincristine, etoposide, the anthracyclines, paclitaxel, cisplatin, and others. The list of generic drugs in short supply across all medical specialties is astounding and includes antibiotics, anesthetic agents, antihypertensive medications, and common electrolyte solutions and vitamins.[1] These shortages, which primarily affect injectable generic drugs, have forced physicians to prioritize patients, improvise standard regimens (substituting capecitabine for 5-fluorouracil, for example, in adjuvant therapy for colorectal cancer), and at times, choose unproven treatment options for patients with curable disease. The National Cancer Institute has watched with increasing concern as common drugs have disappeared from the shelves of cancer-center pharmacies, threatening the completion of research protocols.

The gravity of the problem has provoked a response from oncologists and from governmental agencies. In November 2010, the American Society of Clinical Oncology convened a summit on drug shortages. The Food and Drug Administration (FDA) has set up a special office for collecting information on drug shortages, stepped up its inspection of facilities shut down because of production problems, and loosened requirements for drug importation. Congress has held hearings, and Senators Amy Klobuchar (D-MN) and Robert Casey (D-PA) have proposed legislation requiring early warning of impending shortages from companies anticipating problems with drug supply. On October 21 of this year, the Life Sciences Consortium of the CEO Roundtable on Cancer convened a meeting of interested parties at the Institute of Medicine to consider solutions. Despite all this discussion, no simple answer is in sight, and the number of drugs in short supply grows daily.

The origins of drug shortages are multifactorial, but simply stated, the problem for cancer treatment stems from a confluence of factors: consolidation of generic-drug production in the hands of a few manufacturers (Teva, Bedford, APP Pharmaceuticals, Hospira), who in turn have experienced both increased demand for drugs and production "problems." In general, generic drugs are sold for very limited profit, as fixed by Medicare legislation, and therefore are produced as inexpensively as possible, using older and less efficient production facilities, and with limited inventories to reduce carrying costs for the company. Contamination of commercial

drug vials with particulate or biologic matter has led to the closure of several key plants (Bedford and Hospira).[2]

These plants are being upgraded to comply with FDA standards. The FDA has taken additional measures to expand the drug supply. It has hastened its inspection and approval of new or refurbished facilities and has stated its intent to expedite approval of alternative manufacturers from the United States and abroad. However, the list of drugs in short supply continues to grow. In the face of these production difficulties, there has been suspected stockpiling of scarce drugs by hospitals and by "gray-market" (unofficial, though not necessarily illegal) wholesalers that are out to profit from the sudden unfulfilled demand. To add to these problems, the worldwide demand for oncology drugs is growing rapidly, as Asian, South American, and even African countries expand access to cancer treatment. This trend is likely to exacerbate the shortage and divert supplies abroad.

Are there alternative sources of drugs? There is an extensive untapped capacity to produce generics in Europe and Asia. Major pharmaceutical companies, such as Pfizer and Sanofi, have generic products, many of which are sold exclusively overseas. In recent months, Pfizer has begun to market in the United States two drugs, irinotecan and doxorubicin, that it formerly produced on patent in this country. Sanofi has offered to make its extensive list of common generics available in the United States but has not yet been encouraged to do so by the FDA. Major pharmaceutical companies could re-enter the market for off-patent products, but they need the incentives of a reasonable profit and an expedited route to marketing approval.

A number of long-term remedies, both legislative and regulatory, have been suggested. Although manufacturers cannot be required to produce drugs to meet market demand, congressional hearings have led to calls for requirements for early warning about shortages. Others, including me, have suggested basic changes in the Hatch–Waxman Act of 1984, which set standards for the generic-drug category. We propose that, as a part of a new license application, manufacturers should be required to present projections for product demand and plans for meeting those demands. Legislation could require that a company establish redundancy in its production capacity for generics, just as it does for patented drugs, and could allow the FDA to revoke marketing licenses for companies that fail to meet minimal production goals. Holders of Abbreviated New Drug Application (ANDA) licenses who have effectively met market demand and maintained production should be afforded priority review in the competition for future generic licenses, while the track record of those that fail should be a strong negative factor in consideration of approvals for new applications. Even exclusivity in licensing generic products could be considered. In assessing the growing urgency of the situation, we must keep in mind that some of the current leading patented drugs used in oncology, including granulocyte colony-stimulating factor (G-CSF) and erythropoietin products, will be coming off patent in the next few years, and the problem of providing life-sparing generics will only get worse.

Finally, a greater financial incentive for manufacture of generics would very likely improve industry's track record. Currently, Medicare legislation resets reimbursement for injectable generics at no more than 6% above the average sales price (ASP) paid during the preceding quarter for any given agent.[3] These limits affect price and reimbursement for all purchasers and providers, result in little profit for the manufacturer and the provider in the U.S. market, and

greatly limit the ability of generic-drug manufacturers to increase their prices. Meanwhile, generic drugs manufactured in the United States can be sold abroad for a greater profit. This differential will promote the "leakage" of U.S. drugs to overseas markets.[4] Although the United States can ill afford higher prices for drugs, raising the price of generics, which currently account for less than 2% of the cost of cancer drugs, would have minimal effect on the total cost of cancer care.

On October 31, 2011, in response to the shortages, President Barack Obama issued an executive order in which he broadened reporting requirements for potential shortages and instructed the FDA to accelerate reviews of new applications for marketing of generics and to provide information to the Justice Department about possible collusion or price gouging related to the shortages. This action represents a step forward in addressing this issue. The specific manner in which these orders will be implemented and the degree to which they will ameliorate the drug shortages are unclear. The executive order does not improve reimbursement for generic drugs or address the need for redundant production facilities or incentives such as rewarding past performance in the approval of new generics applications.

It will be up to the community of cancer doctors, patients, and concerned citizens to demand further action at the federal level and by the private sector to ensure access to lifesaving and life-extending drugs. A license to market lifesaving products should entail a public obligation to meet demand. After all, if we can afford to spend billions of dollars on medical research, we should, as a society, enjoy the fruits of that investment by assuring the manufacture of generic drugs.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Massachusetts General Hospital Cancer Center, Boston.

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Finance Committee Hearing on Drug Shortages
Senator Amy Klobuchar Statement for the Record

Chairman Baucus, Ranking Member Hatch, I appreciate the Finance Committee holding this hearing to discuss causes and possible solutions to the drug shortage crisis.

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.

Over a year ago, I 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.

And just a couple of months ago, I met a young boy named Axel Zirbes. Axel Zirbes is a cute four-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, 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 is 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 – a dramatic increase from 55 just five years ago.

For some of these drugs, no substitute drugs 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."

Financial decisions in the pharmaceutical industry are also a major factor.

Many of these medications are in short supply because companies have simply stopped production. They decided it wasn't profitable enough to keep producing them.

Instead of low-priced (and low-profit) generic drugs, companies want to produce and sell more expensive brand name drugs.

Mergers in the drug industry have narrowed the focus of product lines. As a result, some products are discontinued or production is moved to different sites, leading to delays.

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

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.

Earlier this year, I introduced the Preserving Access to Life-Saving Medications Act with Senator Bob Casey of Pennsylvania. The bill would require drug manufactures to provide early notification to the FDA whenever there is a factor that may lead to a shortage.

This will help FDA take the lead in working with pharmacy groups, drug manufacturers and health care providers to better prepare for impending shortages, more effectively manage shortages when they occur, and minimize their impact on patient care.

The legislation would 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 that may result in a shortage.

And 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 two years, the FDA, with early notification and more information, has successfully prevented 137 drug shortages.

To place added pressures on the pharmaceutical industry and to provide additional resources to the FDA, the President issued an Executive Order that will:

- Push drug companies to notify the FDA of any impending shortage of certain prescription drugs,
- Expand FDA's current efforts to expedite review of new manufacturing sites, drug suppliers, and manufacturing changes, and
- Work with the Department of Justice to examine whether drug companies have responded to potential drug shortages by illegally hoarding medications or raising prices to gouge consumers.

This action will help further reduce and prevent drug shortages, protect consumers, and prevent price gouging. This step enhances actions already underway at FDA and puts in place additional tools to address drug shortages.

While the President's Executive Order takes 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 in the Senate 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.

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.

We must ensure that we have the manufacturing capabilities to keep up with demand. As a member of the HELP Committee bipartisan working group, I am working with my colleagues to

determine broad, permanent solutions that can be accomplished through early notification and other improvements at the FDA.

However, as the Chairman and members of the Finance Committee are well aware, we must also consider solutions related to market incentives and payment policy. One solution may be to provide tax incentives to incentivize manufacturers to continue to make drugs that are on the shortage list. Or to provide other market incentives, such as including exclusivity pricing, similar to those we give to manufacturers who make orphan drugs. Another option, which is being discussed at this hearing and among Finance Committee members, is focused on the extent to which changes to payment policy may address the current economic imbalance in the prescription drug market.

In addition, I have 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.

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 bipartisan working group 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.

Statement of Senator John D. Rockefeller IV
Senate Committee on Finance
Hearing on "Drug Shortages: Why They Happen and What They Mean"
December 7, 2011

Thank you for holding this important hearing on prescription drug shortages. I am deeply troubled that, at the same time as we are dealing with an epidemic of overdoses from prescription painkillers, we are also facing a shortage of other kinds of prescription drugs that might be necessary to save someone's life. Both of these problems are impacting West Virginians in very serious ways, and they must be addressed.

Drug shortages pose a serious and growing threat to public health, and in some cases have been life-threatening. It's estimated that 550,000 cancer patients have had to miss or delay their chemotherapy treatments in this year alone, while some antibiotics, intravenous drugs and drugs commonly used for heart patients have been particularly hard for hospitals and pharmacists to find. In fact, according to a survey by the American Hospital Association, almost all hospitals have experienced at least one drug shortage in the past six months. For instance, thirty to forty percent of the oncology patients at one large hospital in West Virginia have been impacted by drug shortages. Another West Virginia hospital reported that they were forced to buy an expensive brand-name colon cancer drug instead of the generic colon cancer drug they otherwise would have used – at more than 10 times the price per dose.

Every state has been and continues to be impacted by the drug shortage problem. However, the problem varies significantly from state to state with some states feeling the drug shortage more acutely than others. According to the IMS Institute for Healthcare Informatics, thirteen states – including my home state of West Virginia – have experienced a sharp decline of 30 percent in monthly per capita usage of the most impacted drugs.

West Virginia hospitals have seen a dramatic increase in frequency and severity of drug shortages for the past two and a half years but with no recourse. While hospitals and pharmacists have borrowed and shared when possible, many health care providers have had to cancel major surgeries and other life-saving procedures due to the lack of necessary drugs. In one stark example of just how bad this problem has become, two young ovarian cancer patients in West Virginia who travelled long distances to reach their hospital were told that they would have to delay starting their treatment because the drug they needed was not available. Drug shortages can also be extremely disruptive to patient care; once a patient has started on a particular treatment protocol it can be extremely risky to change or interrupt that protocol.

One disturbing side effect of the current shortage of many drugs to treat cancer and perform surgery is the parallel "gray market" that has sprung up to take advantage of health care providers' urgent need to treat their patients. As documented in an August 2011 report prepared by the Premier health care alliance, gray market vendors sell drugs that hospitals are not currently able to acquire through their normal distribution networks. These vendors take advantage of supply shortages to sell the drugs at huge markups. In a survey of solicitations that hospitals actually received from gray market vendors in April 2011, Premier found that the gray

market companies were selling drugs to hospitals at prices that were an average of 650% higher than the prices the hospitals normally paid. On top of the fact that these vendors appear to be profiteering from drug shortages, there are also significant concerns about the safety and authenticity of the drugs they sell. I appreciate the attention today's hearing is bringing to this issue, but I think Congress should be doing more to understand how these gray market vendors operate.

For so many Americans this issue is a matter of life or death. I look forward to continuing to work with my colleagues and the appropriate agencies in correcting this problem and restoring trust in our drug supply for patients and their families. I thank the Chair.

Finance Committee Hearing Statement
"Drug Shortages: Why They Happen and What They Mean"
Senator Olympia J. Snowe
December 7, 2011

Thank you, Chairman Baucus and Ranking Member Hatch, for holding this hearing today on drug shortages. Without question, there is a tremendous feeling of frustration among both patients and providers surrounding this chronic issue. In a nation such as ours, with the latest technologies and medical breakthroughs at hand, it seems inconceivable to be faced with a problem of this nature.

At a time when hospitals are trying to achieve greater quality and efficiency, such as better deployment of electronic records, improving care transitions, and exploring the possibility of accountable care organizations, drug shortages are a dangerous distraction. For example, drug shortages have caused Eastern Maine Medical Center to spend an additional $200,000 in drug expenses over the past 12 months to mitigate the shortages due to replacement products that cost more, products bought off contract, out-sourcing, et cetera. In fact, Eastern Maine Medical Center has a pharmacist *specifically assigned* to manage the drug shortages. Other hospitals are turning to outside pharmaceutical compounding companies to manufacture for them – which also increases cost.

At Cary Medical Center in Caribou, the staff hours, including management, dedicated to managing drug shortages has more than doubled over the past couple of years. And at PenBay Medical Center, the hospital has worked to rearrange treatment schedules to have all chemotherapy patients on a certain drug treated on the same day to minimize waste since some of these drugs are only good for 24 hours after reconstitution. Many hospitals are purchasing larger than normal quantities when certain products are available, which only exacerbates shortages elsewhere.

Not only do drug shortages drain vital financial and staffing resources that are best deployed elsewhere, they cause critical patient safety issues as well. According to another hospital in Maine "*The risks of using alternative medications that may have different precautions, doses, or administration procedures than what the staff are used to certainly do exist. I am not aware of any harm that has come to one of our patients but I can point to near misses and delays in therapy*."

While there has been a strong sense of cooperation among providers to help each other out with drug shortages, they also share the same aggravation that "gray market" suppliers are charging anywhere from 10-20 times the normal cost of drug. Providers are wondering aloud why gray market suppliers that specialize in hard to

find drugs can get their hands on these drugs and hospitals can't. At the same time, they have deep concerns about the authenticity of these drugs. Hospitals in Maine are desperately trying to avoid this option of last resort, but as one executive said, "*If faced with a patient in need and no alternatives, I may be forced to hold my nose and do so.*"

So I'm pleased that today's hearing will focus on some of the root causes of drug shortages. Manufacturing problems, raw ingredient shortages, industry consolidation, business decisions and pricing incentives all play a role. President Obama's Executive Order – which requires advanced notification of shortages to the FDA, and increases staffing in FDA's Drug Shortage Program – represents a good first step, but will not be the last word on this multifaceted issue.

I appreciate the bipartisan leadership Chairman Baucus and Ranking Member Hatch are exercising on this critical issue and look forward to hearing from our panelists.

Thank you, Mr. Chairman.

Senate Finance Committee

Hearing on

"Drug Shortages: Why They Happen and What They Mean"

December 7, 2011

Statement for the Record

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Good morning and thank you Chairman Baucus, Ranking Member Hatch, and distinguished Members of the Committee, for holding this hearing. My name is Kasey Thompson and I am Vice President of Policy, Planning and Communications for the American Society of Health-System Pharmacists (ASHP). I am here today to talk about the problem of drug shortages and how shortages are affecting patients and the ability of healthcare providers to care for them.

For the last 10 years, ASHP, in collaboration with the University of Utah drug information program, has been tracking drug shortages, and making that information available to the public on our Web site. We provide a list of shortage drugs, which are defined by the FDA as those for "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." In the past five years, shortages have rapidly escalated, increasing from 70 in 2006 to 231 as of this November, and there appears to be no end in sight. Generic injectable drugs, which are commonly used in hospitals, comprise the majority of drug shortages. Many drugs fundamental and essential to care are in scarce supply, including anesthetics and pain medications, antibiotics, life support drugs for emergency care, and intravenous nutrition.

Because shortages affect our hospitalized and most vulnerable patients, patient safety and quality of care is our primary concern. Without access to the preferred drug treatment, clinicians must use alternatives, which may be less effective or associated with increased risk of adverse outcomes. Examples of these events are described in detail in the Institute for Safe Medication Practices survey in September 2011. In this survey, 1800 respondents reported over 1000 adverse drug events caused by shortages. Twenty-five percent of these reports were medication errors; another 20% were adverse drug reactions. A survey conducted by the American Hospital Association in July 2011 also identified suboptimal care, indicating that 82% of hospitals reported delayed treatment and more than half said they could not provide some patients with the recommended therapy.

Drug shortages also add to the cost of providing care. A study by Premier in March of this year suggested the cost of purchasing alternative therapeutic products to those in shortage to be $200 million. In addition, a survey conducted by ASHP and the University of Michigan indicated that hospital pharmacists are spending 8-12 additional hours per week dealing with shortages. Further, the study estimated that additional annual labor costs to hospitals of managing shortages to be $216 million. Every minute spent dealing with a drug shortage is time taken away from patient care.

In some cases, we are able to determine why there is a shortage, in other cases, we simply have no idea. As a first step we support the passage of the current bipartisan legislation in the House and Senate that would help the FDA prevent some shortages from occurring if they were notified about a manufacturing problem or planned discontinuation. FDA data indicate that 54% of drug shortages are related to product quality problems followed by lack of capacity or other manufacturing issues. About half the time manufacturers do not disclose the reason for a shortage. Our analysis over the last 10 years has shown that many drug shortages are the result of quality issues in the manufacturing process, loss of a manufacturing site, delays and capacity issues, shortages of raw materials-- particularly a single source of an Active Pharmaceutical Ingredient, product discontinuations, and secondary shortages of a therapeutic alternative resulting from a primary shortage. We recognize that there is no one cause of drug shortages, and therefore no one solution.

We are pleased to see that other facets of drug shortages, including economic factors, are being considered, but we are not currently in a position to draw any conclusions given a lack of sound data. A recent report by the Assistant Secretary for Planning and Evaluation describes the economic analysis of drug shortages. It identified a number of possible factors that influence drug shortages and noted that "Shortages have been concentrated in drugs where the volume of sales and drug prices were declining in the years preceding a shortage, suggesting that manufacturers are diverting capacity from shrinking

lines of business to growing ones." It has been suggested that Medicare reimbursement policies may be partially to blame for drug shortages. While we believe this is an area that should be explored further, we are hesitant to focus on any one potential cause given the limited data and the numerous factors that contribute to shortages. It will be important to learn from other stakeholders in the supply chain including pharmaceutical manufacturers, wholesalers, group purchasing organizations, and others in order to fully assess these causes and solutions to this public health crisis.

Other incentives for manufacturers to stay or re-enter the market should be examined. For example, tax credits awarded to companies for developing new technologies in the production process should be explored. We believe that any incentives should be geared toward increasing production capacity and upgrading facilities in order to meet demand for critically important generic injectables.

In conclusion, drug shortages continue to be a very serious public health crisis, and compromise our ability to treat adult and pediatric cancer, to feed newborns intravenously who cannot eat, to relieve pain, to battle serious infections, and provide care when the most appropriate drug is unavailable. While some causes are known, others are not quite as clear. ASHP supports more examination of these other factors to help identify additional causes of drug shortages currently plaguing our healthcare system. We look forward to working with Congress, the FDA, and other stakeholders to ensure an adequate supply of critical, life-saving medications. Again, thank you Mr. Chairman, ranking member, and all members of the committee for the opportunity to provide input on this urgent public health crisis.

Drug Shortages Background and Policy Options

Shortages of prescription drugs in the United States have gained increasing attention in recent years due to the scope and severity of the drugs in short supply. The majority of these shortages occur in drugs that are generic injectables, often administered in a hospital or clinic setting. The shortages have been occurring for anti-cancer drugs, anesthetics, pain, and nutritional drugs, all of which play crucial roles in the care of patients. The result of drug shortages is that caregivers must scramble to find the drug, or use an alternative if one is available. Many caregivers have expressed concern that even if a therapeutic alternative exists, it is likely an older drug which may have more severe side effects or negatively interact with other medications the patient is taking. Further, drug shortages have caused widespread fear among caregivers who are deeply concerned that care could be delayed, rationed, or is provided in a suboptimal manner to stretch doses and preserve scarce supplies.

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

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

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

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

ASHP continues to work with FDA, other health care provider groups and members of the supply chain to address the issue. However, we also believe Congress can help us as well. ASHP supports bipartisan legislation (S. 296, H.R. 2245) that would require drug manufacturers to notify the Agency when they experience an interruption in the production of a drug product potentially resulting in a shortage situation. According to FDA, in 2010 the Agency was able to avoid 38 drug shortages when they were made aware of production interruptions ahead of time, and so far this year, 101 shortages were avoided. However, we believe other steps can be taken as well, for example, require confidential notification of the disruption in supply of single source active pharmaceutical ingredients (API), require manufacturers to develop continuity of supply plans, establish incentives for manufacturers to remain or re-enter the market, and urge FDA to develop expedited approval pathways for pre-1938 (unapproved) drugs. Finally, ASHP believes that FDA must have adequate resources devoted to alleviating and preventing drug shortages.

Notification System

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

The importance of notification is highlighted by quality concerns associated with the increased globalization of pharmaceutical manufacturing. A number of drug shortages can be traced back to quality concerns with foreign-produced APIs. An extreme example was the heparin contamination that occurred in 2007, which resulted in a recall, and a subsequent product shortage that was immediate and continued for an extended duration of time. While FDA has increased foreign inspections, it still lacks the resources necessary to fully address this issue. Therefore, drug shortages precipitated by recalls caused by substandard APIs will continue and likely increase.

Legislation (S. 296/H.R. 2245) in Congress would mandate that companies confidentially notify FDA of the interruption in production of any product six months in advance, or as soon as possible in the event of an unplanned stoppage. Manufacturers that fail to report this information would be subject to civil monetary penalties. This early warning system would allow the agency to communicate more effectively

with manufacturers and others in the supply chain to plan for pending supply interruption. The early warning system should be the cornerstone of congressional action to address drug shortages.

Confidential Notification for Single-Source API

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

Continuity of Supply Plans

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

In 2010, FDA worked with APP Pharmaceuticals to help alleviate a shortage of propofol, a widely used anesthetic preferred by anesthesiologists because of its excellent safety profile compared to other available drugs. By enabling the company to work with its German counterpart to import the drug, FDA was able to substantially improve product availability after the shortage occurred. Using this example, if an acceptable foreign alternative could be identified before a shortage occurs through establishment of

continuity of supply plans for vulnerable drugs, then importation could be expedited and the negative impact of a specific shortage on patient care could be minimized or averted. Importation represents an extreme example of contingency planning. It its simplest form, manufacturing strategies that include collaborating with other manufacturers, establishing back-up suppliers of raw materials and APIs, and creating alternative production capabilities that can be used as countermeasures would be a significant step forward to combating drug shortages. Contingency planning by companies producing drugs critical to patient care must be a standard of practice. S. 296/H.R. 2245 support the development of contingency plans for drugs that are vulnerable to shortages.

Incentives

Further, shortages are occurring overwhelmingly among generic injectable drugs, where production processes tend to be more complex than their solid dosage counterparts. Low margins for these expired patent products coupled with complex manufacturing processes may lead some manufacturers to abandon production of these drugs altogether in favor of products with higher profit margins, thus reducing the number of potential suppliers of products critical to patient care. A way to offset this problem may be to explore incentives to encourage manufacturers to either stay in the market or enter the market with a new product line. More study needs to be conducted to validate the need for incentives. In addition, other stakeholders in the supply chain need to provide input on the economic factors that influence production capability.

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

FDA must find a way to abbreviate and prioritize approval processes for existing therapies that are unapproved, but widely used and essential for patient care. For these drugs, the agency should work with manufacturers to fast track their approval for the U.S. market, especially in cases where the

potential exists for those drugs to fall in short supply. Barriers to manufacturing and marketing these drugs must be minimized in order to foster production and availability of these drugs.

Conclusion

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

ASHP, along with several other stakeholder groups has been working collaboratively with Congress and supply chain stakeholders to develop solutions to the drug shortage problem. As indicated before, there is bipartisan legislation in both houses of Congress. Passage of legislation that provides additional authority to FDA is a step in the right direction. In the long term, FDA will require additional resources to best address this and other issues that impact the quality and safety of drugs.

Figure 1: Total Shortages and oncologic shortages

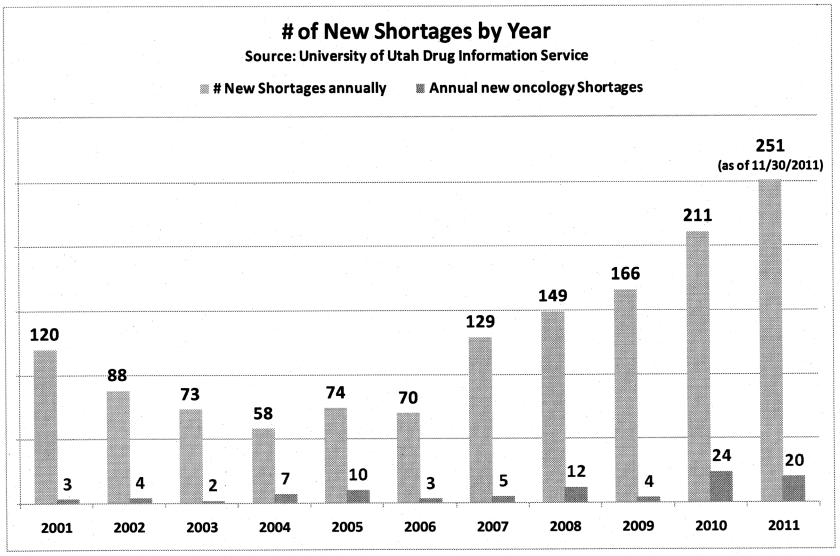


Figure 2: Shortages by drug class

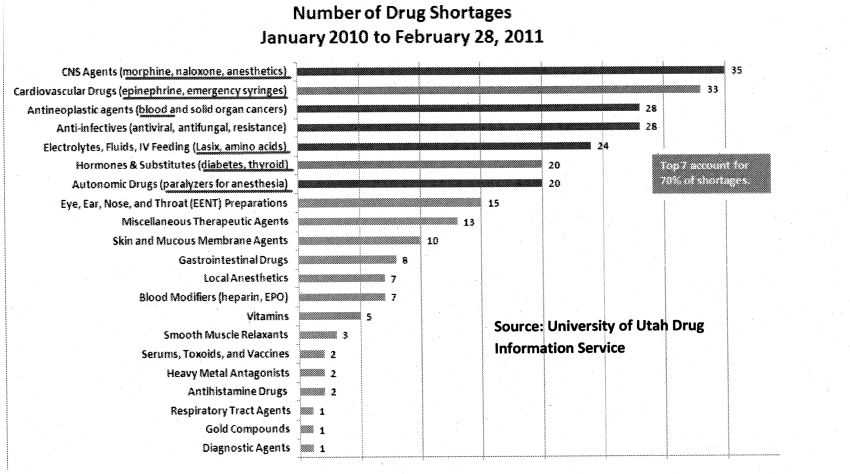


Figure 3: Causes of shortages – FDA data

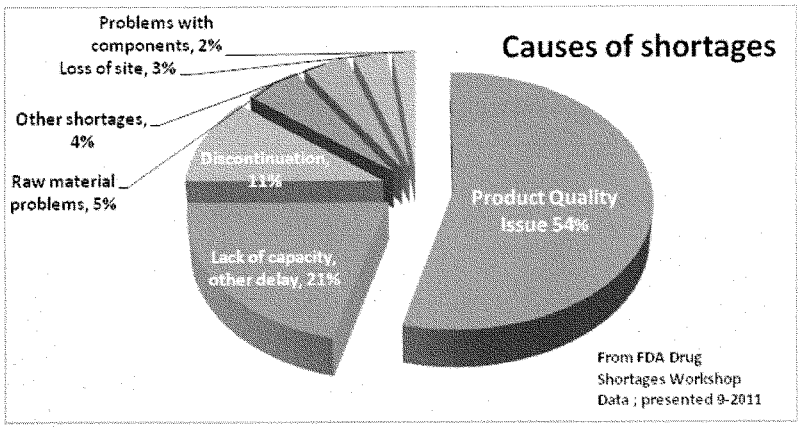
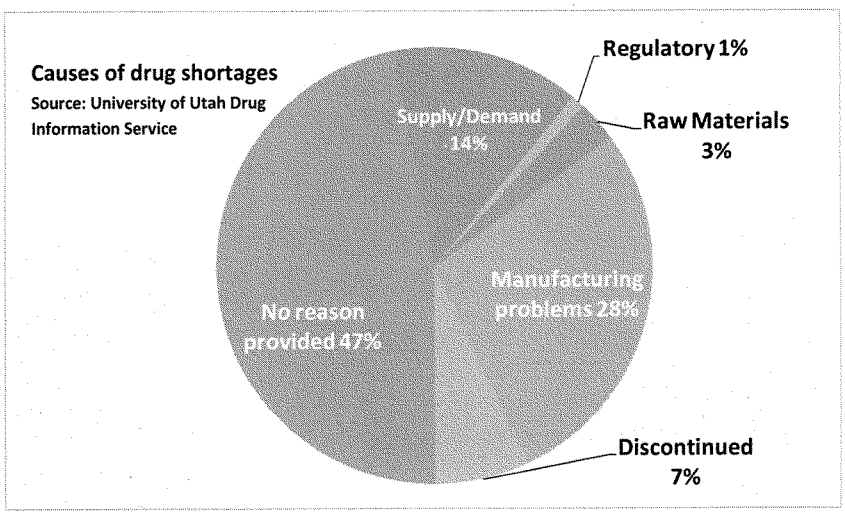


Figure 4: Causes of shortages – University of Utah data



United States Senate Committee on Finance
Public Hearing
"Drug Shortages: Why They Happen and What They Mean"
December 7, 2011

Responses to Questions Submitted for the Record for Kasey Thompson

Senator Olympia J. Snowe

Medicare Pricing

As many of you have observed, there is no silver bullet that will solve the issue of drug shortages. Yet there are some common themes and the majority of you have pointed to problems with Medicare pricing as one of the root causes of this multi-faceted problem. Some of you have also suggested tax credits for companies for developing new technologies in the production process, or other incentives to expand domestic capacity.

1. **Are there savings to be found elsewhere in the area of pharmaceuticals that could help offset the cost of addressing these pricing and reimbursement problems?**

Answer: This may be another question that the manufacturing community is in a better position to provide some meaningful input.

Quality in Manufacturing

Dr. Thompson, in your testimony, you mention that quality issues have risen from the increasing reliance on foreign ingredient and manufacturing sources and the lack of FDA resources to expedite approval of supplemental new drug applications and conduct foreign inspections. In fact, both you and Dr. Gottlieb mention the crisis over adulterated Heparin in China. According to a Pew Health Group report on the aftermath of Heparin, "China is home to the *highest number of sites* subject to FDA inspection outside of the United States, but receives the *lowest levels of oversight* compared to other countries". Most astonishingly, "over an eight year period, the FDA conducted 182 inspections in China (out of 920 total facilities), compared to nearly a combined 900 inspections in Ireland, Switzerland, Italy, France, the United Kingdom and Germany (out of 938 total facilities)". This is despite the fact that E.U. sites are at lower risk for quality and safety issues.

2. **Do you anticipate a growth in quality problems as more drug companies are manufacturing products in China and India? How can FDA and manufacturers stay ahead of quality issues when it comes to foreign inspections, particularly in Asia, where they have failed to keep pace thus far? What are reasonable goals for progress?**

Answer: This is not an area where ASHP has significant expertise but would defer to FDA and other members of the supply chain who may be able to more appropriately address this.

3. **What can be done to better coordinate efforts between the United States and the European Union to more strategically deploy resources.**

Answer: Perhaps FDA can work to coordinate and align European and American drug safety and integrity standards. The Agency itself may have additional input on this.

"Gray Market"

While there has been a strong sense of cooperation among providers to help each other out with drug shortages, they also share the same aggravation that "gray market" suppliers are routinely charging anywhere from 10-20 times the normal cost of drug. Providers are wondering aloud why gray market suppliers that specialize in hard to find drugs can get their hands on these drugs and hospitals can't. For example, at St. Joseph's Hospital, they were short of an IV medication used to treat high blood pressure and heart rate, and there are no good alternatives, so they had no choice but to purchase that drug from a secondary wholesaler. A product that traditionally cost them between $5 to $6 per 10 vials, cost the hospital $120 for that same 10 vials. At Maine General Hospital, they were receiving calls from a secondary wholesaler, offering prices of $476 for a vial of medication that normally cost $4.80/vial.

4. **Are you aware of any current investigations on price gouging of shortage drugs?**

Answer: We are aware of Congressman Elijah Cummings' list of questions sent to several secondary drug wholesalers in response to solicitations from those companies that were made available to his office through a tip-line created to collect that information.

5. **Do we need new authority to reign in abuses by gray market vendors or do we need better enforcement and utilization of the tools we already have?**

Answer: We would like to find out more about this distribution system, such as how they obtain products, why the price differential is often times much higher, and explore whether these suppliers have access to information that the rest of the supply chain does not.

COMMUNICATIONS

STATEMENT FOR THE RECORD

SUBMITTED TO THE

SENATE FINANCE COMMITTEE

ON

Prescription Drug Shortages:
Why They Happen and What they Mean

December 7, 2011

AARP
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For further information, contact:
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Government Affairs

On behalf of our members and all older Americans, AARP commends the Senate Committee on Finance for holding this timely hearing on prescription drug shortages. This issue is of immediate and critical importance to millions of patients and their families who rely upon life sustaining medications that are currently in short supply. As the nation's largest organization representing Americans who are age 50 and older, the drug shortage crisis is of particular concern because older Americans use more prescription drugs than any other age group.

We appreciate the opportunity to highlight our concerns about the toll that the drug shortages are taking on older Americans and to urge you and your colleagues to move swiftly to find solutions that not only address the current shortages but also prevent them from happening again in the future. Individuals who are reliant upon these medications are facing serious impediments to access to the drugs needed to treat deadly diseases. Some are skipping doses in order to extend their supply. Some are being given alternative, far more costly, substitutes. Finally, some are simply being told to wait until the physician's or hospital's supply has been replenished – even if the drug is needed to prevent their illness from worsening.

The drug shortages are also responsible for dangerous lapses in patient safety. The most obvious concerns arise with potential quality problems, such as impurities in the ingredients of drugs that may be purchased from unregulated sources. Less appreciated, however, are the significant safety problems that may arise because the use of substitutes increases the opportunity for prescribing errors. A recent survey from the Institute for Safe Medication Practices found that 25 percent of clinicians noted errors occurred where they practice because of drugs shortages, in part due to clinicians' inexperience with drug products that were used as alternatives because the ones they normally used were not available.

The shortage is placing both patients and their health care providers in a terrible predicament and legislative and administrative action is needed now before the crisis becomes more widespread. Patients who rely on these medications need help. Patients want to know that the drugs that they have been prescribed are available when they need them and that the amounts that costs are fair and affordable.

Unfortunately, drug shortages are nothing new. More than 45,000 different drug products are on the market, produced by an estimated 1,400 different manufacturers. Each year, shortages of some products occur and the Food and Drug Administration (FDA) reports on drug shortages as they become evident. The U.S. now confronts the longest list of shortages in a number of years, increasing from 61 drugs in 2005 to 178 in 2010. What's even more alarming is that some have predicted this list may expand to as many as 280 drugs by year's end.[1]

Of course, of greater concern than the number of products considered to be in short supply is the nature of these products. Many drugs in short supply are of critical clinical importance. They are used to support or sustain life or to prevent debilitating disease.

While sterile injectible drugs make up a small share of the overall prescription drug market, they made up 80 percent of the products on the current shortage list and include drugs to treat certain types of cancer and anesthetize patients in surgery and treat their pain.[2] Other drugs in short supply include those to treat cardiovascular disease, central nervous system conditions and standard remedies used in hospital emergency rooms, such as certain antibiotics.[3] About 80 percent of the drugs in short supply are generic drugs. This is of particular concern because branded therapeutic substitutes, if available, are much more expensive to purchase.

Our concerns about the impact of the drug shortage may best be illustrated by looking at two of the categories of drugs for which current shortages exist and which disproportionately harm older Americans: chemotherapy drugs used to treat certain cancers, as well as drugs used for anesthesia and pain control related to surgery.

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[1] U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Issue Brief: Economic Analysis of the Causes of Drug Shortages, http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.pdf; Ted Agres, Nagging Drug Shortages Defy o Easy Fixes, *Anesthesiology News*, November 2011, www.anesthesiologynews.com/ViewArticle.aspx?d=Policy+%26+Management&d_id=3&i=November+2011&i_id=785&a_id=19639.

[2] IMS Institute for Healthcare Informatics, Drugs Shortages: A Closer Look at Products, Suppliers and Volume Volatility, November 2011. www.imshealth.com/portal/site/ims/menuitem.edb2b81823f67dab41d84b903208c22a/?vgnextoid=a6fbcc0f68f73310VgnVCM100000ed152ca2RCRD&vgnextfmt=default&vgnextrefresh=1#.TtpJE9zceSs.email.

[3] Id.

About 10 to 11 percent of the drugs on the shortage list as of the fall of 2011 are used to treat cancer.[4] Although cancer is a disease of all ages, about 78% of all cancers are diagnosed in persons 55 years of age and older.[5] Some of the most common types of cancer in adults, including breast and colon cancer, are treatable if they are caught early enough. Indeed, thanks to improvements in cancer treatment, many types of cancer are now regarded as chronic illnesses. (As of 2006, the five year survival rate was nearly 70 percent).[6] But cancer treatment often relies on consistently taking one or more chemotherapy drugs, and some of these drugs are the ones for which the worst shortages exist.

Patients and their health care providers confront a myriad of difficulties in the event that a specific chemotherapy drug is in short supply. When a cancer treatment center runs out of a given drug, they or their patients may be able to find another center that has the drug available. The patient then has to travel to a less convenient location to get treatment. For patients in smaller and in particular more rural communities this can mean traveling far distances which could be more than a simple inconvenience if the patient is already frail. Some may not have access to transportation. Skipping treatments is reportedly a common response to these challenges, and because chemotherapy regimens are carefully timed to maximize effectiveness, missing one or more treatments can have serious consequences.

Less publicized, but just as troubling, is the effect of the drug shortages on clinical trials, often focused on new treatments for cancer. Many trials require testing a new drug against an older product. When the older products are no longer available, then the trial cannot continue. For example, 7 out of 42 clinical trials being conducted at an Atlanta-based cancer institute have been affected because of the shortage of one drug.[7]

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[4] Stacy Simon, Cancer Drug Shortages Concern Doctors and Patients, American Cancer Society News, www.cancer.org/Cancer/news/News/chemotherapy-drug-shortages-concern-doctors-and-patients

[5] American Cancer Society, Cancer Facts and Figures, 2011, www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011 www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029771.pdf

[6] Id.

[7] Id.

The shortage of drugs used for surgical anesthesia also poses risks for older patients as well as surgical patients more generally.[8] Surgical centers, both inside and outside of hospitals, are forced to adopt strategies that consume valuable time and resources in order to serve their patients properly. More importantly, there are indications that in some facilities, the safety and quality of patient care are at risk.[9] If manufacturers and suppliers fail to provide advance warning of a shortage, then the problems can be particularly severe because health care providers do not have time to preserve existing supplies or seek out alternative sources. When shortages reach a crisis, surgeries may have to be delayed or canceled. As in the case of cancer drugs, alternative drugs may be prescribed, but they are often far more expensive and may be less effective. For example, to treat pain, some surgical patients are being prescribed IV Tylenol in lieu of certain generic narcotics, a much more expensive and sometimes less effective option.

The substitution of anesthetic drugs can also produce complications that necessitate additional medical services. In a recent survey conducted by the American Society of Anesthesiologists, 48% of 1,373 anesthesiologist respondents said the shortage of anesthesia-related drugs had compromised "optimal patient outcome." Examples included "prolonged awakening, longer stays in the recovery room and increased nausea and vomiting, but there have been reports of significant adverse events, including deaths in some critically ill patients."[10]

The recent increase of drug shortages is not just harming patients who need medications; it is also costly to the healthcare system as whole. Steps taken by hospitals and physicians in responding to shortages divert precious resources away from delivering and improving care. For example, it was reported that the additional labor costs associated with drug shortages in 2010, when the problem was less severe, was $216 million.[11] These are costs that are already being shouldered today in the absence of a pandemic or natural or other catastrophe, when both the financial and human toll could be enormous.

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[8] See, Medical News Today, Surgical drug Shortage Might Undermine Patient Safety, November 30, 2011, www.medicalnewstoday.com/articles/238467.php.

[9] Hopkins, Thomas J. et al. Use of a Multidisciplinary Drug Shortage Response Team (MDSRT) to Prevent Adverse Impact From a Succinylcholine Shortage, American Society of Anesthesiologists Annual Meeting 2011, Abstracts, www.asaabstracts.com/strands/asaabstracts/abstract.htm;jsessionid=5A5DE631ED59ADC9D13F2577B820DD4E?year=2011&index=15&absnum=6282.

[10] Ted Agres, Nagging Drug Shortages Defy Easy Fixes, Anesthesiology News, November 2011, www.anesthesiologynews.com/ViewArticle.aspx?d=Policy+%26+Management&d_id=3&i=November+2011&i_id=785&a_id=19639.

[11] Id.

The issue of drug shortages is one that has the potential to impact the entire health care system. AARP appreciates that the reasons for the current drug shortage problem are many and complex. There is no sole cause of this problem; thus, there is no single solution to address it. Many different solutions will have to be employed, some of which are outside the scope of the Senate Finance Committee; AARP has identified several policy proposals the Senate Finance Committee could adopt to help address this problem.

Medicare Coverage of Alternative Drugs: Where alternative supplies of a specific drug are not available, a patient's physician may have to prescribe a therapeutic substitute, if one exists. In some cases, switching to a substitute often means replacing a generic product with a much more expensive brand name product. For example, the brand drug, Abraxane, costs 19 times as much as the generic drug paclitaxel, even though the generic may be just as effective in treating breast, lung or ovarian cancer.[12]

Approximately 80 percent of the drugs in short supply are generic drugs, indicating that providers may often be forced to prescribe a branded, more expensive product to patients. AARP strongly urges CMS to amend its coverage rules to provide coverage for alternative drugs when the standard drug is in shortage or no longer available. In cases where the initial drug is deemed to be a drug that is in short supply,[13] beneficiary cost-sharing should be the lesser of the cost-sharing associated with the initial drugs vs. the cost-sharing associated with the substituted drug.

Possible Changes to Medicare Reimbursement: It has been suggested that Medicare reimbursement is a contributing factor to the drug shortage problem. The Medicare Modernization Act (MMA) of 2003 requires Medicare to reimburse physicians for prescription drugs based on the drug's average sales price, which is a price determined by the market decisions of manufacturers. This system has effectively limited manufacturers' ability to raise prices, making it difficult to attract manufacturers when shortages emerge.[14]

If strong evidence emerges that Medicare reimbursement is a major contributing factor to prescription drug shortages, AARP believes that CMS should explore alternative reimbursement options. However, CMS should be mindful that any changes to reimbursement rates will likely have downstream effects on Medicare and the health care system overall. CMS should also be mindful of the potential impacts on beneficiary out-of-pocket costs. Approximately half of seniors are living on incomes of roughly $20,000 or less per year and pay an average of $4,241 in annual out-of-pocket health care costs. Many Medicare patients, already living on fixed incomes with little margin for added expenses, cannot

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[12] The average wholesale price for paclitaxel is $312 for a dose compared with $5,824 for Abraxene. Gatesman and Smith, November 9, 2011.

[13] The FDA defines a drug shortage as a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level.

[14] E. Emanuel, "Shortchanging Cancer Patients," *New York Times*, August 6, 2011.

easily absorb higher cost-sharing for expensive drugs, indirectly discouraging utilization.

Adequate staffing: As Congress and others develop ways to address this problem in the long-term, beginning immediately in cases where it is determined that a drug is or will soon be in short supply, HHS should work with all relevant agencies and stakeholders to determine the best course of action to address drug shortages. Given that older Americans utilize drugs more than any other segment of the population, CMS should also be part of this task force.

CONCLUSION

Clearly, the current level of drug shortages cannot and should not be permitted to persist. Nor should it be allowed to happen again. The President's Executive Order issued in October marks a good first step by ensuring that the FDA and the public will receive adequate notice of when a manufacturer is discontinuing production of its drugs in one or more of its facilities that could lead to supply shortages. The new authority given to the FDA will help it work with manufacturers to address the causes of the shortages and also lead to a better early warning system for hospitals, doctors and patients so that they can make alternative arrangements before the shortage becomes a crisis.[15] It should also lead to more government scrutiny of efforts by market participants to stockpile drugs in short supply or to engage in price gouging.

However, given the multiple factors at play in creating drug shortages, additional steps will likely be needed to address the drug shortage problem. AARP welcomes the intensified focus being given to the issue through this Committee's hearing and other hearings across Capitol Hill. We hope that your findings will inform bipartisan solutions that can be speedily implemented so patients no longer experience the anxiety of not knowing when or where their next dose of a drug will come from or whether they will be able to afford it. AARP looks forward to working with the members of this Committee to develop and promote solutions to the drug shortage crisis.

Once again, we thank you for holding this important hearing focusing on the issue of prescription drug shortages. Just as there is no one cause of the problem, we recognize that there is no single solution. We stand ready to work with this Committee, all Members of Congress, Executive Agencies, and other stakeholders to implement solutions which are of critical importance to millions of patients and their families.

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[15] The White House, Executive Order. Reducing Prescription Drug Shortages, October 31, 2011.

American Society of Anesthesiologists

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Drug Shortages: Why They Happen and What They Mean
United States Senate Committee on Finance
Wednesday, December 7, 2011

Statement for the Record by
Jerry A Cohen, M.D., President of the 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 Baucus and Ranking Member Hatch for holding a hearing regarding drug shortages on December 7, 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 Finance 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 of 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% of anesthesiologists altered a procedure in some way, 48% felt shortages resulted in a less optimal patient outcome, 48% reported longer operating room or recovery times and 10% postponed or cancelled procedures. While these numbers may be alarming they pale in comparison to the 98% of anesthesiologists who experienced a drug shortage during the past year, or the 90% 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% 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 of 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.[i]

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 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.

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%. However, for propofol the average markup is a startling 3,161%.[ii] 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 Finance 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.

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[i] *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.

[ii] 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/Gray-Market-Analysis-08152011.pdf

AMERICAN SOCIETY OF HEMATOLOGY
2021 L Street, NW, Suite 900, Washington, DC 20036 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

"DRUG SHORTAGES: WHY THEY HAPPEN AND WHAT THEY MEAN"

COMMITTTEE ON FINANCE
UNITED STATES SENATE
DECEMBER 7, 2011

WRITTEN STATEMENT

SUBMITTED FOR THE RECORD

BY THE

AMERICAN SOCIETY OF HEMATOLOGY

Attention: Editorial and Document Section
Dirksen Senate Office Building, Room 219
Washington, DC 20510-6200

On behalf of the American Society of Hematology (ASH), thank you for conducting a Senate Finance Committee hearing on "Drug Shortages: Why They Happen and What They Mean." ASH's comments describe how drug shortages are affecting hematologists and the patients we treat, including: rationing of care, increased costs, and disruption of clinical research. In addition, these comments offer several recommendations for strategies to combat drug shortages. Drug shortages of life-saving medications have become a national crisis requiring urgent attention and ASH urges Congress to work with stakeholders, including the Society, to identify and implement effective strategies to prevent patient harm and disruptions in patient care.

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases, including blood cancers such as leukemia, lymphoma, and myeloma and a number of nonmalignant illnesses such as anemia (including sickle cell and thalassemia), thrombosis (including venous thrombosis, heart attack and stroke), and bleeding disorders. The patients our members treat have been especially adversely affected by recent shortages. For example, early this spring, a national shortage of cytarabine, an irreplaceable chemotherapy drug essential to the cure of acute myeloid leukemia (AML), was reported. (Cytarabine cures forty percent of patients with AML; without cytarabine, the cure rate is zero percent. This shortage affected thousands of patients who were diagnosed with AML and treated in the approximately 6-month period when cytabine was out of stock.) Currently, we face a shortage of another important drug in AML, daunorubicin. In the intervening months, scores of other leukemia, lymphoma and myeloma patients also faced shortages of life-saving treatment. Additionally, our sickle cell patients have struggled with a lack of access to hydroxyurea, the only approved drug used to treat this disease. In all of these cases, the patients may not have been able to be treated or received less effective or more toxic alternative treatments, not because of a lack of insurance coverage or because the treatment was too costly or because their doctors did not know how to treat their disease, but, rather, because the standard treatment was simply not available.

Although physicians have dealt with national drug shortages before, the increasing number of shortages of drugs in the United States has become critical and life threatening. Each year the total number of new shortages identified has increased. Between 2006 and 2010, the number of new drug shortages tripled. What is even more alarming is that we continue to see increasing numbers of shortages this year. According to the University of Utah Drug Information Service, there were 211 reported drug shortages for calendar year 2010. As of November 30, 2011, there have been more than 250 reported drug shortages. If the current trend continues, it is estimated that up to 300 drugs will be, or have been, in short supply by the end of this year, an increase of approximately one-third.

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

companies may be tempted to redirect resources to more profitable products, and financial return may not justify corrective action when problems occur.

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

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

The interruption in treatment caused by shortages puts vulnerable patients at risk. Physicians have been forced to send some of their most fragile patients to hospitals, pharmacies and clinics in geographically inconvenient locations to access remaining supplies of their therapy.

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

The cost implications of such shortages can be considerable. Traditionally, practitioners have been proactive in controlling health care costs by using generic drugs. Because of drug shortages, however, practices have been forced to choose more expensive alternative treatments. Recently, another cost issue has occurred—this one involving Medicare beneficiary cost sharing. The Society has heard from physicians and patients who have been denied Medicare coverage because they had to receive an alternative, more expensive therapy when the standard drug was not available due to a drug shortage.

Drug shortages have also adversely affected clinical trials that are pivotal in research and treatment efforts. Trial activation has been suspended and patient accrual halted, ultimately slowing the pace of clinical research. For instance, a recently opened large Eastern Cooperative

Oncology Group (ECOG) randomized clinical trial in Acute Myeloid Leukemia involving cytarabine and daunorubicin could not accrue patients and delayed the research.

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

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

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

- **Improve FDA Communication with Stakeholders** – Information provided by the FDA, pharmaceutical companies, and medical societies about shortages frequently varies. The inconsistencies can be confusing to stakeholders and can complicate the management of patients. ASH recommends that the FDA increase its current communication with the pharmaceutical industry and medical societies to ensure that timely and accurate information is being delivered to all stakeholders. One basic way to improve and enhance communication would be to develop specialty-specific listservs. Any information that the

FDA receives about a potential shortage could be filtered through the relevant listserv to all stakeholders. Also, if drug companies and medical societies are circulating information, they could share this information through the relevant listserv as well. This should include information regarding specific drugs in shortage, length of time, and ways physicians may access therapies in short supply. This practice would ensure that all stakeholders receive accurate information in real time.

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

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

- **Provide Economic Incentives to Manufacturers of Critical Drugs** – Many shortages have occurred because manufacturers are having a difficult time maintaining a profit margin for lower cost generic drugs. Consequently, several people have begun to look at how to provide economic incentives to manufacturers of these products in order to prevent shortages. ASH believes this has potential to help address the problem of drug shortages and supports further study. While some have suggested changing the current Average Sales Price (ASP) formula as one means to accomplish this, ASH notes that ASP is a measure of reimbursement for physicians, not price. The ASP may not be an adequate reimbursement system and may need to be changed, but this is a different issue than providing economic incentives to manufacturers and does not address the drug shortage problem. Another approach that may be more effective would be to expand "orphan drug" status to incentivize production of specific low cost critical drugs. The Society recommends further study of this option.

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

Thank you for your consideration of ASH's comments and recommendations. The Society looks forward to working with you on this urgent and most important issue. Please contact ASH Senior Director of Government Relations, Practice and Scientific Affairs, Mila Becker (*mbecker@hematology.org* or 202-776-0544), if the Society can provide additional information or expertise.

Comments for the Record

United States Senate Committee on Finance

Hearing: Drug Shortages: Why They Happen and What They Mean

December 7, 2011, 10:00 AM
215 Dirksen Senate Office Building

by Michael G. Bindner
The Center for Fiscal Equity
4 Canterbury Square, Suite 302
Alexandria, Virginia 22304

Chairman Baucus and Ranking Member Hatch, thank you for the opportunity to address this topic. Our response will be within the context of our four part tax proposal, which includes a VAT to fund discretionary spending, payroll taxes to fund Old Age and Survivors Insurance, an income surtax on higher income individuals and families to fund overseas military deployments, debt reduction and net interest and a Net Business Receipts Tax to fund social spending, including health. We will not duplicate witness statements that lay out the problem, except to assert that the largest driver of drug shortages is an uneven relationship between drug manufacturers and consumers.

One feature of the NBRT is that it allows employers to fund health plans for workers and retirees or provide direct services in lieu of paying taxes so that individual benefits can be funded. Of course, in a single payer or public option environment, the government would be the 800 pound gorilla driving negotiations with drug companies to guarantee the availability of drugs and disbarring any companies that engage in price gouging.

One feature of the NBRT, either with single-payer or without it, is that employers could be given an incentive to offer alternative care arrangements, either a better plan than is available under single-payer or direct care with staff physicians, contract facilities and contract specialists for employees and even retirees as an offset to a portion of the NBRT payment. This feature provides an incentive for significant cost savings.

Employers who fund catastrophic care or operate nursing care facilities would get an even higher benefit, with the proviso that any care so provided be superior to the care available through Medicaid.

Making employers responsible for most costs and for all cost savings allows them to use some market power to get both lower prices for drugs and the ability to demand that lower cost drugs be available – leverage that individuals just don't have.

This proposal is probably the most promising way to arrest health care costs from their current upward spiral – as employers who would be financially responsible for this care through taxes would have a real incentive to limit spending in a way that individual taxpayers simply do not have the means or incentive to exercise.

While not all employers would participate, those who do would dramatically alter the market. In addition, a kind of beneficiary exchange could be established so that participating employers might trade credits for the funding of former employees who retired elsewhere, so that no one must pay unduly for the medical costs of workers who spent the majority of their careers in the service of other employers.

Thank you for the opportunity to address the committee. We are, of course, available for direct testimony or to answer questions by members and staff.

From: Anne M. Dranginis, Ph.D.

December 19, 2011

To: Senate Committee on Finance

Washington, DC 20510-6200

Re: Senate Finance Committee Hearing "Drug Shortages: Why They Happen and What They Mean", December 7, 2011

I wish to submit this statement for the record of the hearing on the shortages of critical drugs. I have been a biomedical researcher for my entire adult life. For eight years I was a scientist at the National Institutes of Health in Bethesda Maryland and for twenty years I have been a professor of biological sciences at St. John's University in New York City. A year and a half ago I was diagnosed with ovarian cancer. I would be taking Doxil, one of the most powerful of the chemotherapies for this type of cancer, if it were available but unfortunately Johnson and Johnson has stopped manufacturing it, forcing me to turn to less effective drugs with worse side effects.

In a free market another manufacturer could step in to take advantage of the unavailability of Doxil and other life-saving drugs that are in short supply. For several reasons there is no longer a free market in these drugs. In the case of Doxil, Johnson and Johnson sought and won extended patent protection under the Orphan Drug Act. They have the exclusive right to manufacture Doxil until 2014 but they aren't making it, thus endangering the lives of the over 7,000 people who were depending on it and bringing to a halt many of the 30 clinical trials that require it.

Most of the drugs in short supply are generics with low profit margins, while the most expensive drugs rarely have these "production problems". According to an article in March in Business Week (1), the operating margins of Johnson and Johnson have grown considerably, from 17.7 percent in 1990 to 26.8 percent in 2010, and they have 28 billion dollars in cash. One might think this would be enough to fix production problems and resume saving lives.

However according to a recent article in the NY Times (2) many drug companies are having difficulty finding ways to profitably invest their hoards of cash. Instead of investing in research or improving their production facilities they are laying off scientists and using their cash to buy back their stock. This inflates the earnings per share of the stock by simply reducing the number of shares. Coincidentally, executive compensation is often pegged to increases in earnings per share. Since 2006 Johnson and Johnson has bought back 23.5 billion dollars worth of its own stock while laying off over 10% of its workforce (3).

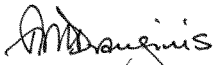
As a taxpayer and a scientist I have contributed to the development of the basic science and drug discovery necessary to the continuing profitability of the drug companies. I do not believe they should have the right to maintain patent protection on critically needed drugs that they cannot or will not provide. There has been a total lack of

transparency from Johnson and Johnson on this situation. They are endangering lives and yet they do not seem to be accountable.

The ovarian cancer patients who have been abandoned by Johnson and Johnson are America's mothers, sisters and daughters. Most of us know someone with this disease. Our president's mother died of it. How can they just shut off the supplies of life-saving drugs? The consolidation of the drug companies has resulted in powerful monopolies that increasingly do not serve the public interest

(1) http://www.businessweek.com/magazine/content/11_15/b4223064555570.htm
(2) http://www.nytimes.com/2011/11/22/business/rash-to-some-stock-buybacks-are-on-the-rise.html?pagewanted=1&_r=1&sq=pfizer&st=Search&scp=2
(3) http://www.fool.com/investing/value/2011/07/12/what-does-johnson-johnson-do-with-its-free-cash.aspx

Signed,



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8 December 2011

Via Federal Express
Honorable Max Baucus
Chairman
Honorable Orrin G. Hatch
Ranking Member
Committee on Finance
United States Senate
Room SD 219 Dirksen Office Bldg.
Washington, D.C. 20510-6200

Re: Hearings on Drug Shortages

Dear Senators Baucus and Hatch:

My dear friend and client Daniel V. Schiavello of New Jersey has been sentenced to death by Johnson and Johnson's unwillingness to compel production of Doxil, a lifesaving chemotherapy drug.

At yesterday's hearing, the Committee heard various reasons for the drug shortage. In the case of Doxil, Johnson and Johnson has offered a litany of excuses including quality control and manufacturing issues, but the fact remains that while the finger pointing occurs, people for whom this drug remains the only hope are dying.

Johnson and Johnson licenses Ben Venue Labs, a subsidiary of the giant German company Boehringer. Months ago Johnson and Johnson knew of problems. They created a wait list for the drug while telling people that they were working with a substitute manufacturer they refused to name. Now with perhaps thousands of women for whom Doxil remains a primary Ovarian cancer treatment risking death by Christmas, Johnson and Johnson stonewalls patients and suddenly the posted information on the Doxil website is strangely silent about the future of Doxil.

We wonder why Johnson and Johnson doesn't terminate the license it gave Boehringer and relicense another manufacturer? If Donald Trump were involved, he would have fired the manufacturer a long time ago for breach and sued for damages on behalf of all affected patients while finding a new licensee. Why hasn't Johnson and Johnson taken action?

We wonder why the FDA which grants an exclusive monopoly on the drug doesn't step in and order the continued production of Doxil with a consent decree?

We wonder why the FDA won't grant a compassionate use waiver allowing patients to import the drug from foreign sources for their personal use. The FDA claims the drug is on the approved manufacturing list so a waiver is not available but what good does being on the list do if no one is manufacturing it?

We also wonder about Johnson and Johnson's motives when we are told by a foreign resource we found that they were pressured by Johnson and Johnson not to ship to the United States in direct contravention of a commitment I had from the Company that they would not block our efforts?

We refer you to a Fox News special that aired this morning on yesterday's hearing, the drug shortage in general, and Mr. Schiavello's case in particular. The link to the video may be found at: http://video.foxnews.com/v/1315875725001/

We would hope that the Committee would urge the FDA to take prompt action so that lives will not be lost while the companies involved argue over profit and blame.

We are enclosing Mr. Schiavello's testimony plus my letter to a Johnson and Johnson director for inclusion in the record.

Respectfully submitted,

Martin P. Klein

C: Messrs. Russell Sullivan & Kolan Davis

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12 November 2011

Via Federal Express
Mr. Leo F. Mullin

Dear Leo:

I recall with affection our friendship while you were with Delta and I am writing you in that spirit, but also in your capacity as a director of Johnson & Johnson and chair of its public policy committee. I urgently need your help to save a life and to do right by Johnson & Johnson.

The subject is the availability of a chemotherapy drug called Doxil and how to correct a manifest injustice. I am puzzled about the morality of recent business decisions by Johnson & Johnson and its responsibility to provide lifesaving Doxil for the 4,500 patients that desperately need this chemotherapy to stay alive.

I am enclosing a copy of my earlier letter to William Weldon of Johnson & Johnson that I wrote on behalf of my friend and client, Daniel Schiavello. I suspect the letter was never forwarded to you. The reply was shameful. It gave no answers at all. Instead it requested me to disclose my personal health records so I could be put on the Doxil wait list. Rather than seeking to resolve the matter, it appears that Johnson & Johnson desires to exacerbate it and that is symptomatic of what I believe to be inherent problems within the Company and which have caused increased private litigation, litigation by regulators and the government, consent decrees, deferred prosecution agreements and much more.

In an effort once again to resolve this matter, permit me to share some facts with you.

Dan has been battling Leiomyosarcoma that has metastasized to his lungs. He has been treated with Doxil for over four years. Incredibly, with only Two days notice before his last scheduled chemotherapy treatment, he was advised that Doxil would not be available to him at any time in the near future. Not only was there tremendous anxiety for both physician and patient, but also as the Company notes itself, withdrawal of Doxil exposes a patient to very serious risks apart from the return of the cancer, including a 50% risk of serious cardiac failure.

Dan should be a "poster boy" touting the success of Doxil. Instead the Company's conduct effectively amounts to a death sentence for him, without any reasonable time to find an alternative viable therapy. In his case, it is truly a medical emergency for him to get his Doxil treatment as soon as possible.

When he was being treated with other chemotherapy drugs, his tumors were increasing in size and number. While on Doxil, he has seen significant and continuous reduction (over 85%) in tumor size. During the past two years, the days between his Doxil cycles have been significantly increased and his Doxil dosage has been significantly reduced to help moderate toxicity side effects. He is now at the minimum dosage intensity. With his current dosage at a minimum and the time between treatments lengthened, any interruption in treatment could be fatal. Also, multiple oncologists have told him that he is not a good candidate for any other currently available alternative chemotherapy drug.

Dan considers himself to be among a fortunate group of perhaps 10% of diagnosed Leiomyosarcoma patients who have survived five years or more and he is probably among a smaller group of patients that have been taking Doxil for more than four years. One would think, as a long time patient on Doxil with such great results, that Janssen would be interested in his outcome and that he would be among the last patients to be deprived of the drug, especially since he is now taking the minimum dosage intensity of Doxil.

I am sure you would agree that two days notice of the withdrawal of the only lifesaving drug is not legally sufficient or morally defensible. Yet the situation is even worse. In August, Dan was told that while there was a Doxil shortage, existing patients did not have to register for the new Doxil cares program. He was assured by his physician that he would continue to receive the lifesaving medication. Approximately two weeks later he was informed by his physician that he had been given the wrong instructions by Doxil cares and the Janssen drug representative. Now all patients were required to register and by this time, Dan was chronologically behind on the registration list.

I cannot believe the Company is so disorganized yet this is symptomatic of what I believe to be the way the Doxil cares program was created and is being implemented by, I believe, an outside contractor.

Had he been given accurate information, Dan would have immediately insisted that his oncologist sign him up for the program. However without any notification of urgency, Dan's oncologist did not sign him up until 19 days after the program was implemented. My client does not have an alternative to Doxil except to anticipate his demise.

Johnson & Johnson refuses to provide Dan with any information. Despite efforts, Johnson & Johnson refuses to disclose even where he is on the wait-list and if and when it expects to produce enough Doxil to remove him from the list. One would hope that Johnson & Johnson is not insisting on litigation and its discovery process as the prerequisite for disclosure of lifesaving information. As a shareholder, that would trouble me greatly.

We believe that Doxil cares has been contractually obligated to restrict and intentionally withhold truthful information regarding (1) information as to the patient status on the Doxil cares waiting list; (2) specific Doxil production dates and amounts; (3) specific delivery dates to Janssen's distributors and (4) the amount of Doxil sold to grey market distributors by Ben Venue, thereby removing that pre-sold grey market inventory from distribution via the Doxil cares program.

Every one of these patients deserves this information. The physicians need to know if there is no Doxil forthcoming so they can arrange for patients to go to Israel or Canada for Myocet, a similar drug as yet unapproved in the U.S. It is morally wrong for this lifesaving Doxil to be withheld and even more immoral to leave patients and doctors hanging, waiting with huge anxiety because they have no information to make decisions or take alternative actions.

Doxil, as you may know, is perhaps, the most widely used drug for women with stage four breast and ovarian cancer and certain sarcoma cancers like Lieosarcoma which Dan has been battling. All these patients remain in the dark, many without viable alternatives. Are they to be left to die? Is Johnson & Johnson to be known as the company that withheld lifesaving information from patients?

Interestingly, and in my opinion, it might be advanced that Johnson & Johnson and/or Janssen were being less than candid and consistent with their various statements. Previously Janssen indicated that it "...fully anticipate(s) a smooth, seamless process for our transition to a new manufacturer for Doxil" and "(F)urther we have identified a potential alternative supplier." See September 23, 2011 letter from Janssen Products, LP to Healthcare Providers.

In its latest pronouncement, Rob Bazemore, President of Janssen notes, "(W)e are ultimately accountable and take full responsibility for the (Doxil) shortage and its ultimate resolution." While that statement has all sorts of legal connotations, what's strangely missing is any mention of a new, substitute manufacturer of Doxil, the patent for which, I believe, ends in February 2012.

With thousands of lives in the balance, Johnson & Johnson and Janssen rely upon, in my opinion, the inherently flawed Doxil cares program that has no monitoring or transparency and it is denying my client's right to access his own personal health information and preventing him from making appropriate medical decisions that make the difference of whether he lives or dies.

With no meaningful reply forthcoming from Johnson & Johnson, Janssen or Ben Venue, we have embarked on a public campaign to right a terrible wrong. We are supported by a network of professional pharmaceutical investigative reporters who feel an urgency to work together. We have been joined by Fox News which has produced and aired numerous investigative special reports. Dow Jones has run targeted Doxil shortage stories in the Wall Street Journal. Other leading investigative reporters are now producing personal stories about individuals in their communities who are suffering from the lack of information as well as the tragic termination of their Doxil treatment.

We have appealed to numerous members of Congress and a House subcommittee has just held a hearing on the issue of drug shortages. We have appealed to state government representatives to help rectify this crisis. We've discussed it with the various organizations representing the pharmaceutical industry and others in Washington. More public appeals are upcoming.

We believe Doxil is manufactured by BenVenue a subsidiary of the German company Boehringer and that they wish to exit the contract manufacturing business. Johnson & Johnson claimed it had another manufacturer but refuses to disclose the name of any substitute manufacturer and when product will be available. We believe that documents regarding technological transfer of certain Doxil proprietary rights have been in preparation. Patients ought to have transparency. Without transparency, patients and their physicians remain uninformed. We believe that Doxil may not be forthcoming for months, or even years as FDA approvals for a new facility may take that long.

Of great concern to us is information we just learned this afternoon. We have heard from a reliable source that Ben Venue has not only stopped making Doxil but has retooled the vats and other production facilities for production of another drug. If this information is correct, in our opinion it calls into question many of the prior statement made by Johnson & Johnson and/or Janssen as well as the credibility of the entire Doxil cares program. Desperately ill patients, by virtue of the Doxil cares wait list, may, in our opinion, be given false hope that Doxil production will resume shortly. It would, in our opinion, call for the closest of scrutiny by the appropriate authorities. Lives are at stake and decisions are being made based upon what we believe is either non-disclosure of relevant information, or inaccurate disclosure.

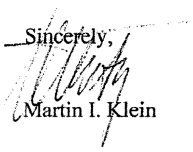
I am familiar with Johnson & Johnson, its history, current litigation and recent settlements. I am hoping to have a word with the FDA Commissioner very soon. I do not believe Janssen's explanations posted on their doxil.com website and their statements are, in my opinion, both insulting and threatening to my client and others whose lives depend on Doxil.

Having spent three years working for the U.S. Senate Health Subcommittee, I believe I have a keen familiarity with the issues involved. I am not anxious to either make this a crusade or to start litigation on behalf of the many affected patients. However there now seems to be a mobilization of public condemnation against a public company that takes "ultimate responsibility" for, perhaps, ultimately taking more lives than were lost on September 11, especially if that taking were on account of financial reasons.

I will continue to advocate and seek alternative solutions for Doxil for the 4,500 men, women and children who are at risk of dying at Christmas. Some need financial assistance to travel to Canada where Medicare and U.S. insurance will not cover Myocet. Perhaps instead of Doxil cares, Johnson & Johnson could truly show it cares by arranging for such assistance.

Whether liability ultimately attaches to Johnson & Johnson, Janssen, BenVenue, Boehringer or a combination of these entities, someone has made a significant error that will cause a life to be lost. I intend to correct that error and save that life. I am going to correct this wrong and do what's necessary to obtain six months of Doxil for Dan Schiavello or pursue whatever recourse we have to require Johnson & Johnson to provide him with Myocet therapy in Canada. I hope you will help.

Sincerely,



Martin I. Klein

NAMD
National Association of
Medicaid Directors

Statement for the Record

By Matt Salo

Executive Director

National Association of Medicaid Directors

United States Senate Committee on Finance

Hearing Titled: ***"Drug Shortages: Why They Happen and What They Mean"***

Wednesday, December 7

Chairman Baucus, Ranking Member Hatch, and members of the Senate Finance Committee, thank you for this opportunity to submit a statement for the record regarding the December 7, 2011 hearing titled *"Drug Shortages: Why They Happen and What They Mean."*

Medicaid

Medicaid is the nation's health care safety net. Jointly financed by the states and the federal government, Medicaid will spend more than $400 billion this year to provide health care to more than 60 million Americans. In 2009, Medicaid spent $25.4 billion in federal and state funds for prescription drugs, excluding managed care spending and specialty drugs covered under the program's medical benefit. The program is administered by the states within a broad federal framework which leads to enormous variation across states in terms of who is covered, what services are provided, and how those services are delivered and paid for. Furthermore, within any given state, Medicaid's role is broad, varied, and complex. Medicaid funds more than 40 percent of all births, and the majority of all publicly financed long-term care in this country. It also provides most of the nation's funding for HIV/AIDS related treatments, mental health services, and others. It is therefore very difficult to talk simplistically about Medicaid (either nationally, or within a state), despite its incredible importance in the U.S. health care system.

NAMD is a newly formed organization created with the sole purpose of providing a home for the nation's Medicaid Directors and we represent all 56 of the state, territorial and DC agency heads. Our two broad objectives are to give the Medicaid Directors a strong, unified voice on national and federal matters as well as helping develop a robust body of technical assistance and best practices for them to improve their own programs. While no two programs look exactly alike, the Directors are unified in their heartfelt desire to improve the health and health care of the growing number of Americans who rely on the program.

Medicaid Drug Rebate Program

The Medicaid Drug Rebate Program, created by the Omnibus Reconciliation Act of 1990 (OBRA '90) which added Section 1927 to the Social Security Act (the Act), became effective on January 1, 1991. The program was enacted out of concern for the cost to the Medicaid program for outpatient drugs. It affords state Medicaid programs the ability to reimburse pharmacies for drugs at market rates while allowing Medicaid to achieve net

costs on par with those offered by pharmaceutical manufacturers to large purchasers. While not the only cause, the Medicaid Drug Rebate Program has helped generate significant savings for the states and the federal government that helps offset Medicaid prescription drug expenditures for outpatient prescription drugs.

The Medicaid Drug Rebate Program is a partnership between CMS, state Medicaid agencies, and participating drug manufacturers. Manufacturers who wish their products to be eligible for coverage by Medicaid must first sign a rebate agreement with CMS and also enter into agreements with two other federal programs – a pricing agreement for the Section 340B Drug Pricing Program and a master agreement with the Secretary of Veterans Affairs for the Federal Supply Schedule. It is worth emphasizing that the Medicaid Drug Rebate Program is a partnership in which manufacturers voluntarily and willingly participate.

According to information posted on the website of the Centers for Medicare and Medicaid Services (CMS), approximately 600 drug manufacturers currently participate in this program. While technically an optional benefit, all fifty states and the District of Columbia cover prescription drugs under the Medicaid Drug Rebate Program.

Addressing Drug Shortages

Medicaid Directors share your concern about the rise in the number of drug shortages over the last five years. State Medicaid agencies are particularly attuned to whether such shortages may impact the quality, efficiency and cost effectiveness of care that is delivered. According to the Food and Drug Administration's October 31, 2011, report, "A Review of FDA's Approach to Medical Product Shortages," this increase was due at least in part to the FDA's augmented efforts to encourage manufacturers to report shortages.

We concur with the witnesses' statements during this hearing that the root causes of drug shortages are unique to each particular medication, multifactorial, and highly complex in nature. Overall, some of the most common reasons cited for shortages include the unavailability of raw ingredients, manufacturing quality issues and FDA enforcement actions that halt production, voluntary recalls, poor inventory ordering, industry consolidation, offshore production, a change in product formulation and even rumors of an impending shortage. In addition, witnesses at this and related hearings have indicated that some drug manufacturers report they have exited the business of making older, generic injectable drugs, which typically are not as profitable as newer, brand-name medicines.

We also strongly agree with the witnesses and other experts who have stated that the potential solutions must be appropriately targeted, based on sound data that any given solution would minimize shortages in the future, and demonstrate that they will not have an adverse impact on other facets of the health care marketplace, including the Medicaid program. Some proposals discussed by this and other congressional committees have suggested implicating the Medicaid Drug Rebate Program in the solution for addressing drug shortages, yet NAMD and our members are not aware of any credible data that would support such a policy.

In fact, we question the soundness of tying rebates, at least in part, to manufacturers exiting the business of making older, generic injectable drugs. These products, which typically are not as profitable as newer brand-name medicines, are commonly not even subject to Medicaid drug rebates as they are given in the hospital on the inpatient side. For the few that are subject to Medicaid drug rebates, the fact that they are generic should minimize the actual cost impact to the manufacturer since generics have a very low percentage Medicaid rebate (13 percent of average manufacturer price). Therefore, if over 90 percent of an injectable is used on the inpatient side, an exemption from the Medicaid drug rebate would provide a 1 percent of AMP impact for the manufacturer. Given the minimal financial benefit for the generics to the manufacturer, this is likely to correlate to a minimal financial impact for the state *provided* the bill was specific to drugs that are in short supply due to halting of manufacturing because of low profit potential.

Medicaid Directors oppose establishing a partial or full exemption from the Medicaid Drug Rebate Program for manufacturers. The drug rebate program was created to address a specific problem and trend in the Medicaid program – to control public spending and ensure states receive discounts similar to those provided to private purchasers. Providing exceptions to the Medicaid Drug Rebate Program to help solve the drug shortage issue, even if temporary in nature, could be very detrimental and disruptive to Medicaid programs.

We respectfully request that the Committee consider several issues prior to advancing legislative solutions impacting Medicaid. For example, we ask that policymakers consider the administrative costs to CMS, states and manufacturers, to implement any Medicaid related proposal, including the ongoing costs for tracking and oversight of proposals for a "holiday" from the drug rebate program.

In addition, we believe policy solutions must consider that a promise to provide a product is *not* immediate and *cannot* be accomplished if the shortage is due to raw material issues. In fact, several of our state members informed NAMD that the shortages

that affect their Medicaid programs are largely raw material shortages due to Drug Enforcement Agency (DEA) allocation.

Simply put, it is ill-conceived to seek solutions from a Medicaid policy that is successfully addressing the problems it was intended to mitigate.

Conclusion

In closing, we respectfully ask that Congress engage Medicaid Directors, through our association, in discussing their experience with drug shortages in order to fully assess these causes and solutions to this public health crisis. Working together we can craft appropriate solutions targeted to the actual problem and that do not create unforeseen consequences down the road.

What to Do about Drug Shortages

Statement for the Record

by

Devon M. Herrick, Ph.D.

Senior Fellow

National Center for Policy Analysis

Submitted to the

Committee on Finance

United States Senate

Drug Shortages: Why They Happen and What They Mean

December 7, 2011

Mr. Chairman and members of the committee, I am Devon Herrick, senior fellow at the National Center for Policy Analysis, a nonprofit, nonpartisan public policy research organization dedicated to developing and promoting private alternatives to government regulation and control, solving problems by relying on the strength of the competitive, entrepreneurial private sector. I appreciate the opportunity to submit this statement for the record.

American hospitals and physicians are facing an unprecedented shortage of commonly used drugs. President Obama announced his support for legislation to address this problem by requiring drug makers to notify the Food and Drug Administration (FDA) of possible shortages six months in advance.[1]

The president also signed an executive order directing the FDA to streamline the process of approving changes to production lines and giving the Justice Department authority directive to investigate alleged price gouging.[2] However, these steps will not fix the drug shortage problem and could even make it worse.

The Drug Shortage Problem Is Real. Drug shortages are widespread. In a recent survey, nine-in-ten anesthesiologists reported experiencing a shortage of at least one anesthesia drug.[3] Oncologists also face drug shortages — in August 2011, more than 40 percent of the 34 generic oncology drugs on the market were in short supply.[4] There are no reliable substitutes for most of these drugs. Most are generic injectable medications that have been on the market a long time and are commonly used in hospitals, emergency rooms and cancer treatment centers.

The American Hospital Association recently reported that virtually all the community hospitals it surveyed had experienced a drug shortage in the previous six months. Nearly half had experienced a shortage of more than 20 drugs in the previous six months. Consider:

- Two-thirds of hospitals surveyed had experienced a shortage of cancer drugs.
- Eighty-eight percent were short on pain medications.
- Ninety-five percent experienced a shortage of anesthesia drugs for a surgery.

Hospitals have responded in a variety of ways, including delaying treatment, giving patients less effective drugs and providing a different course of treatment than the one recommended. Indeed, about 82 percent of hospitals surveyed reported at least occasionally delaying a treatment because of a drug in short supply.

The Drug Shortage Problem Is Not New. The number of newly reported drug shortages has been growing:[5]

- There were 74 newly reported drug shortages in 2005.
- The number dipped slightly to 70 in 2006, then rose to 129 in 2007, 149 in 2008, 166 in 2009, and 211 in 2010.

In mid-2011 there were about 246 shortages.

In 2005, hospitals and clinics complained to Health and Human Services Secretary Michael Leavitt that drug manufacturers and distributors were often out of certain drugs because distributors first filled their more lucrative commercial orders.[6]

Problem: Government Regulation. There are many reasons for drug shortages. Shortages of certain drugs reoccur due to a lack of competition and manufacturing problems.[7] According to former White House advisor and oncologist Ezekiel Emanuel, only about 10 percent of shortages are due to a lack of raw materials needed to manufacture them. The ultimate cause is government regulatory policy. Normally, when a product's price rises due to its scarcity, new competitors enter the market, increasing supply and driving down the price. However, government regulations often prevent price rises that would attract competitors.

Problem: Output Controls. The FDA has stepped up its efforts to ensure that drug manufacturing processes and facilities meet its quality standards by instituting a "zero tolerance" policy. It levies fines and forces manufacturers to retool both domestic and foreign facilities. For example, the FDA approves how much a drug manufacturer can produce. If a shortage develops because the FDA shuts down a competitor's plant, a manufacturer must seek FDA approval to increase its output and alter its production timetable. This slows down adjustments in production.

The Drug Enforcement Agency (DEA) has a role because minute quantities of controlled substances are often used to make other drugs.[8] Its regulations are also inflexible. For example, if a shortage develops, a manufacturer that has reached its preauthorized production cap cannot respond by increasing output without DEA approval.

Problem: Medicare Part B Price Controls. Certain generic drugs are in short supply due to a lack of competition and manufacturing problems, but according to former White House advisor and oncologist Ezekiel Emanuel only about 10 percent of shortages are due to a lack of raw materials.[7] A major cause is government price controls. Normally, the market price of a product rises when it is short supply, attracting competing manufacturers. However, the Medicare Modernization Act of 2003 limited the amount by which the price of the drug could rise over a given period. As a result, says Emanuel, many life-saving generic oncology drugs are scarce. Razor-thin profit margins for generic injectable drugs encourage drug makers to cease production or switch to making more lucrative branded drugs.

The law also changed the way injectable and intravenous drugs administered by physicians are reimbursed under Medicare Part B. Rather than paying providers a fee that varies with the difficulty of the procedure, Medicare reimburses them 6 percent of the drug's cost, based on its average selling price. This gives physicians an incentive to use newer patented drugs, even when older generic drugs are just as effective. Additionally, because of the shortages, says Emanuel, physicians have in some cases substituted new drugs that prolong life a few months when older generic drugs that could cure a patient are unavailable.

Problem: 340B Price Controls. Also contributing to the problem of shortages is the little known federal 340B drug rebate program. This program forces drug manufacturers to give discounts to hospitals and clinics that treat a high number of indigent or Medicaid patients, Public Health Service hospitals and clinics, and certain Federally Qualified Health Centers. Currently, the law requires drug companies to give these hospitals and clinics a 23.1 percent

rebate off of their average manufacturer's price for brand-name drugs and 13 percent for generic drugs on qualifying outpatient use.[9] The Patient Protection and Affordable Care Act (PPACA) — the new federal health care law — will expand the number of hospitals and clinics that qualify for rebates. The number of participating facilities has already grown from about 8,000 in 2002 to more than 14,000 by 2010. It is estimated that nearly 20,000 are eligible under the PPACA.[10] According to a U.S. Government Accountability Office report, nearly one-third of U.S. hospitals qualify for 340B drug discounts.[11]

Furthermore, manufacturers are not allowed to increase brand-name drug prices faster than the Consumer Price Index. If they do, the drug maker has to rebate the excess amount above the Index. This means manufacturers have little incentive to purchase new equipment to maintain or improve their manufacturing processes. As a result, some drugs become less and less profitable over time.

Responses to Drug Shortages. Economics teaches that when prices are kept artificially low, shortages develop. People adjust to persistent shortages in ways that can worsen the shortages.

Stockpiling. Buyers typically respond by hoarding drugs when the supply is uncertain. A As a report from the Premier healthcare alliance, a consulting firm, explains, "Drug shortages have been exacerbated by stockpiling on the part of providers," who are trying to "protect themselves from the instability of the drug supply chain by placing orders that exceed normal requirements."[12] Occasionally, the unit rebate exceeds the average manufacturing price of a drug. Rather than requiring manufacturers to rebate more than the price of the drug, the FDA created a "penny price policy," allowing the manufacturer to charge a minimum price of one penny per dose. When a drug is in short supply, a drug maker must restrict sales to a proportion of past purchases in order to prevent 340B-eligible facilities from hoarding or reselling drugs worth far more than the price they paid.

Black Markets. Shortages also lead to the development of black (or gray) markets, where speculators buy a drug in short supply and sell it for a much higher price. An additional problem with the development of black markets is the potential sale of expired drugs of dubious origin. Finally, wholesale drugs can pass from one distributor to another, resulting in multiple transfers with higher prices at each point.[13] In August 2011, members of the Premier healthcare alliance report paying "gray market" prices as much as 335 percent above the approved rate.

Cascading Effects on Other Markets. Shortages in one market tend to cascade to others. In general, when hospitals cannot get a drug, they will turn to the next best alternative. But as the Premier healthcare alliance analysis explains, when a shortage of one drug increases demand for a therapeutically similar product, the substitute may also become scarce because it "is not normally produced in quantities sufficient to meet unanticipated market needs."[14] This happened last year when a shortage of morphine lead to a shortage of the substitute painkiller hydromorphone.

Solutions. Attempts to solve drug shortages with more regulations could actually worsen the problem. Indeed, expanding the number and type of companies required to provide advance

notice of impending shortages would *exacerbate* shortages by encouraging hospitals to hoard drugs.[15] Such legislation would not make it any easier for manufacturers to avoid the problem.

Ultimately, the only way to alleviate the drug shortage is to make generic drugs more profitable. Thus, Congress should create a mechanism to reduce rebates for specific drugs in short supply. For example, injectable drugs are harder to store and involve different manufacturing processes, handling and administration than do simple tablets. Therefore, injectable drug rebates should be lower.[16] Congress should also reform regulations that reimburse physicians a percentage of a drug's cost for administering it, rather than a fee schedule based on the complexity of the procedure.

Furthermore, Emanuel and other policy analysts say injectable generic drugs should be reimbursed under Medicare Part D private drug plans rather than Part B. Competing drug plans have kept drug costs lower than they would be otherwise, and have helped maintain adequate supplies of covered drugs.

In addition, Congress should reward new investments in the manufacturing process. Limiting price increases for Part B drugs to increases in the Consumer Price Index often means that it is unprofitable to upgrade older production facilities. The federal government cannot expect firms to make necessary upgrades if profit margins do not cover costs.

Finally, regulation of production processes should be more flexible. Drug makers that want to boost production are often delayed by the approval process. For example, the FDA currently requires a triple-check verification of the manufacturing process over an extended time period.

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POLICY SOLUTIONS FOR DRUG SHORTAGES

Statement for the Record

submitted by

St. Jude Children's Research Hospital

for the

United States Senate Committee on Finance

Hearing on Drug Shortages: Why They Happen and What They Mean

December 7, 2011

St. Jude Children's Research Hospital ("St Jude") appreciates the opportunity to submit this statement for the record, which reflects our views on the drug shortage crisis in the United States, particularly as it affects children's hospitals like St. Jude.

St. Jude, located in Memphis, Tennessee, is internationally recognized for its pioneering research and treatment of children with cancer and other life-threatening diseases. The hospital's research has helped push overall survival rates for childhood cancer from less than 20 percent when the institution opened in 1962 to almost 80 percent today. It is the first and only National Cancer Institute-designated Comprehensive Cancer Center devoted solely to children, and no family ever pays St. Jude for care.

St. Jude has experienced drug shortages for pediatric patients over many years. In 2005 and 2006, our experiences with shortages of chemotherapy for pediatric cancer were noted in the national media.[1,2] Throughout much of the 2000s, St. Jude generally experienced only one to five shortages a month. At times these shortages were challenging, but their relative rarity did not create the problems for patient care and research that we now face.

However, the number of shortages at St. Jude increased dramatically in early 2010, and since early 2011, St. Jude has had difficulty obtaining approximately 50 different drugs we use to treat our pediatric patients. On any given day in 2011, approximately 10 to 20 drugs on the St. Jude formulary have been in short supply. The majority of the drugs in short supply at St. Jude have been generic sterile injectable drugs, including injectable nutrition, antimicrobials and chemotherapy drugs used to cure pediatric cancers. Analysis of national shortage data has shown that drug shortages are highly concentrated on generic sterile injectable drugs.[3]

Chemotherapy shortages are a particular concern for St. Jude, and often alternative chemotherapy may not exist, or there may be little or no evidence that alternative drug therapies will be effective in pediatric cancer patients. The most common childhood cancer is acute

lymphoblastic leukemia ("ALL"), with approximately 3,000 cases per year. Approximately 90 percent of patients with ALL can be cured using a combination of up to 10 drugs. **Over the last decade, however, eight of these 10 drugs have become difficult, and at times impossible, to obtain.**

Over the last two years, St. Jude has noticed a marked increase in chemotherapy drug shortages, —both at our hospital and across the nation. In 2010, there were no fewer than 23 national chemotherapy drug shortages. This was the most national chemotherapy drug shortages reported since national data collection started in 2003. In other years, there have been five to 10 chemotherapy drug shortages per year.

Drug shortages, especially chemotherapy drug shortages, have also adversely impacted clinical research at St. Jude and across the country.[4] We are aware that at least 85 Children's Oncology Group ("COG") and 150 National Cancer Institute ("NCI") clinical trials for cancer have been affected by drug shortages. In some cases, clinical trials for cancer patients have been suspended due to drug shortages. At St. Jude, we have not had to discontinue any of our clinical trials due to drug shortages, but there have been times when we have had to carefully consider whether we could continue to enroll patients for certain protocols. Besides limiting clinical trial enrollment, drug shortages have added complexity to the conduct of clinical trials. St. Jude developed guidance for our investigators about how to handle the impact of drug shortages on existing trials, and in some cases, investigators were forced to make substantial protocol amendments.

Our position is that any drug shortage is one too many because it may needlessly threaten the survival of a child with curable cancer. The growing number of drug shortages in the United States has a devastating effect on many patients and demands swift action by Congress and other concerned stakeholders.

Causes of Drug Shortages

Drug shortages may occur for a variety of reasons, such as:

- raw and bulk material unavailability,
- manufacturing difficulties and regulatory issues,
- voluntary recalls,
- change in product formulation or manufacturer,
- manufacturers' production decisions and economics,
- industry consolidations,
- inventory practices,
- unexpected increases in demand and shifts in clinical practice, and
- natural disasters.[5]

Recently, some public health experts have suggested that drug shortages are caused primarily by economics and reimbursement policies. For instance, a November 2011 article published in the *New England Journal of Medicine* explored the economics of branded drugs versus generic drugs, which may serve as a disincentive for the production of generic products and may make oncologists less likely to prescribe and use generic cancer drugs.[6] The U.S. Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation released an issue brief in October 2011 about the economics of drug shortages, finding that neither the quantity of drugs needed by consumers nor the quantity produced by manufacturers are responsive to short-term changes in price.[7] While St. Jude believes that economics play a role in drug shortages, the causes of drug shortages are complex and go well beyond economics.

The federal 340B program drug discount program for indigent patients has been implicated by some analysts as a substantial cause of drug shortages. The primary argument is simply that the number of 340B entities and the number of drug shortages have increased over the same period. However, despite its recent growth, the 340B program remains small relative to the pharmaceutical market as a whole. The 340B program accounts for only two percent of the over $300 billion spent on prescription drugs in the United States. Further, drug shortages are concentrated on generic sterile injectable drugs that frequently are used in the inpatient setting, but the 340B program is limited to the outpatient setting. St. Jude believes it is difficult to attribute a relatively small program for indigent patients in the outpatient setting as the primary cause of drug shortages.

In September 2011, the Food and Drug Administration ("FDA") reported during the Drug Shortage Public Workshop that **more than half of drug shortages are due to serious product quality issues, including particulates, contaminates and impurities.**[8] According to some experts, it seems that the challenges of substandard and counterfeit medications around the globe unfortunately may be contributing to current drug shortages, as well.[9]

In a recent Government Accountability Office (GAO) report, manufacturing challenges for generic sterile injectable drugs were highlighted as a major cause of drug shortages.[10] Manufacturing difficulties occur more frequently for sterile injectable drugs because these drugs are more complex to manufacture compared to other medications.

In summary, the pharmaceutical market is complex, and the causes of drug shortages are varied. While economics and reimbursement policy may play a role in drug shortages, St. Jude does not believe it to be a primary cause of shortages.

Policy Options and Solutions

Given the many reasons drug shortages occur and the complexity of the medication use process, the issue requires multiple responses from multiple actors. St. Jude supports the findings and recommendations from the November 2010 drug shortages summit convened by the American Society of Health-System Pharmacists, the Institute for Safe Medication Practices, the American Society of Anesthesiologists (ASA) and the American Society of Clinical Oncology (ASCO). The recommendations from this summit include solutions from many perspectives: regulatory,

legislative, raw materials, manufacturing, the market and the drug distribution system.[11] Following are a few of these recommendations.

- **Manufacturer notification when a company is leaving the market or curtailing production.** While manufacturer notification to FDA would not be a permanent solution to the current drug shortage crisis, FDA has demonstrated that it has the ability to help avoid shortages when it is notified of conditions that tend to lead to—or at least exacerbate—shortages. In 2010, FDA averted 38 shortages when manufacturers voluntarily communicated potential issues. Further, FDA reported that it helped stave off 99 shortages in the first 10 months of 2011 alone.[12]

- **Mandatory manufacturer notification to FDA of conditions that could result in a drug shortage.** Notification should occur when there is a single provider of the active pharmaceutical ingredient ("API"), which indicates a drug is at a higher risk of shortage and that FDA should monitor it more closely. St. Jude further supports notification to FDA when there is any interruption in the supply of raw materials, API or manufacturing processes. Increasing manufacturer and FDA communication will provide FDA more tools to manage and prevent drugs shortages. The October 2011 Executive Order on drug shortages[13] enhances FDA's ability to prevent and mitigate drug shortages, consistent with current law, but legislation is necessary to codify and formalize FDA's authority to take action to prevent drug shortages.

- **No change in Average Sales Price (ASP) reimbursement or 340B program drugs that are in short supply.** Some analysts have overlaid the growth in 340B entities and changes in reimbursement methodologies with increases in drug shortages and have implied that these programs are a cause of drug shortages. St. Jude urges great caution: changes to these programs may be coincident with the rise in drug shortages, but there is scant evidence that the programs *cause* shortages. It has been shown that the overall supply of products in a drug shortage is unresponsive to price changes, and St. Jude is concerned that these changes in ASP or in reimbursement for 340B drugs would be ineffective and penalize entities that have no role in causing drug shortages.

  It is particularly important that changes in the 340B program are not made as a solution for drug shortages. If 340B prices are suspended for drugs in short supply, entities that provide care for indigent patients would be forced to buy these essential drugs at much higher costs. Specifically, per 340B guidelines, St. Jude would not be allowed to purchase these drugs at our group purchasing organization ("GPO") price. Instead, St. Jude would be required to purchase these drugs at the much higher wholesale acquisition price ("WAC"). Therefore, entities that serve indigent patients would bear the brunt of a problem they did not create or cause, and this policy change likely would have minimal or no effect on alleviating drug shortages.

Given the extent of the drug shortage challenge and the negative impact on patient care, St. Jude also supports more aggressive actions, such as:

- **Incentivizing the production of critical drugs that regularly are in short supply.** The federal government has supported several incentives to spur certain drug development,

such as Orphan Drug Act incentives for the development of drugs that treat rare diseases and conditions. Additional manufacturing capacity for generic sterile injectable products would help alleviate drug shortages over the long term. Congress should consider creating incentives that would spur production capacity for generic sterile injectable products, many of which have been subject to drug shortages in the past several years. In addition to efforts to increase manufacturing capacity, it has been estimated that it may take up to seven years for a new manufacturing plant to come on line, and so action should be taken to reduce the time for a new generic sterile injectable plant to reach production.

- **Developing national stockpiles of key drugs prone to shortages.** National stockpiles of vaccines and other drugs already exist, and the model could be replicated for chemotherapy and other life-saving drugs. Details such as criteria for stockpiling and funding would need to be determined.

- **Importation should be considered as a limited solution to drug shortages.** Importation should be considered carefully and used only on a case-by-case basis when a severe shortage exists and FDA verifies that a foreign drug meets United States manufacturing standards. In select situations, importation has been helpful in alleviating drug shortages, but importation is not a viable long-term solution to drug shortages. St. Jude shares the concerns held by many about the purity and quality of drug product from outside the United States, and we believe that great care must be taken so that counterfeit and dangerous drugs are not imported in place of a drug in short supply.

While these solutions may be more complex and costly, St. Jude believes these steps are necessary to address our country's ongoing drug shortage challenge.

Conclusion

In conclusion, although St. Jude does not believe that drug shortages can be eliminated altogether, health care providers would be able to better prepare and respond to drug shortages with advance notice of conditions that are likely to lead to drug shortages. St. Jude recommends that the FDA be given the authority to require a drug manufacturer to send notification before curtailing or stopping production of a drug product and also to notify the FDA when the manufacturer becomes aware of conditions that are likely to lead to a drug shortage. There should be no change in Average Sales Price (ASP) or reimbursement for 340B program drugs that are in short supply as these actions would likely be ineffective and act to penalize entities that have no role in causing drug shortages. Additionally, Congress should consider incentivizing increased capacity for the development and production of drug products, such as sterile injectable products, that are prone to drug shortages.

Thank you for accepting St. Jude's statement for the record. For additional information, please contact Clinton Hermes, Senior Vice President and Chief Legal Officer at St. Jude, Clinton.Hermes@stjude.org.

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Statement of Daniel V. Schiavello Submitted to the United States Senate Committee on Finance
in Connection with its Inquiry into the Nation's Drug Shortage
December 7, 2011

Submitted by Daniel V. Schiavello
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I have been battling Leiomyosarcoma while on Doxil for over four years. Incredibly, with only two days notice before my next scheduled chemotherapy, I was advised that Doxil would not be available to me at any time in the near future.

Prior to being treated with Doxil, my tumors were increasing in size and number while on other chemo drugs. While on Doxil, I have seen significant and continuous reduction in tumor size. Additionally, during the past two years, the days between my Doxil cycles have been significantly increased and my Doxil dosage has been significantly reduced to help moderate toxicity side effects. I am now at the minimum dosage intensity. With my current dosage at a minimum and the time between treatments lengthened, any interruption in treatment could result in disease progression or drug resistance, both potentially fatal. In addition, it has been documented by the drug manufacturer that discontinuing Doxil treatments after prolonged use may potentially cause fatal cardiac side effects.

This effectively amounts to a death sentence for me, without any reasonable time to find an alternative viable therapy.

On August 5th Janssen, a division of J&J, sent out a letter requesting that healthcare providers register their patients for the Doxil CARES program. I have since obtained a copy of that letter and there was no sense of urgency indicated in it. Prior to this letter, Healthcare providers were told that only new patients would be affected.

On August 24th, I was told, by my oncologist's office, that an application was being filed on my behalf, as part of the Doxil CARES program, and that it was just procedural. It was the first time I was ever informed of such a program. It was reinforced to me that I should not be concerned because my September 1st. scheduled chemotherapy treatment was not affected. On August 30th, I was called by my oncologist and told that my appointment was being postponed because there was no Doxil available for me. I was also told that I was on an indefinite waitlist and that they have not received any shipments of Doxil since August 9th.

My application was submitted 19 days later than the announcement date. I was never been given a chance to advocate on my own behalf since I was totally uninformed about the process. Although I wish that my application was filed sooner, I believe my healthcare provider acted in good faith because they assumed that this was just a bureaucratic procedure and they were also not properly informed about the crisis.

After speaking to many representatives of J&J, I learned that the current production allotment of Doxil was allocated by the end of the day that the program was announced. Any additional Doxil CARES applications were put on a wait list. They informed me that the criterion for distributing Doxil is only on a first come-first serve basis without exceptions for medical urgency or necessity. It essentially became a race to the fax machine by oncologists all over the country. I have since learned that there are over 2000 patients on this waitlist. When I requested to know where my name is on the waitlist, I was informed that this information was not being released. I other words, patients scheduled for a treatment on August 5th may have Doxil on reserve if their Oncologist filed their paperwork while patients scheduled at a much later date on a more critical timeline are being denied treatment

I also have learned that many distributors and hospitals throughout the country have ample supply of Doxil because there were "tipped off" about the pending crisis. A J&J

representative also acknowledged that they expected hoarding by healthcare providers. Unfortunately, these other healthcare providers are unwilling or unable to "share" their Doxil with other healthcare providers that do not have and any Doxil inventory. They also will not accept new patients for treatments because they claim that it is not in accordance with the Doxil CARES program rules. In my case, I was told that there is available Doxil with ten miles of my home but I have been declared ineligible to receive the drug at those facilities because I would be considered a "new patient".

I have also inquired about a compassionate drug use waiver with my local Congressional office. I was told that Doxil does not qualify for compassionate use since it is an approved drug even though it is unavailable in the USA. One alternative was to purchase the drug out of the country, smuggle it back into the USA and then find someone to administer it to me while risking the potential for a contaminated or counterfeit drug.

I consider myself to be among a fortunate group of perhaps 10% of diagnosed Leiomyosarcoma patients who have survived five years or more and I am probably among a smaller group of patients that have been taking Doxil for more than four years. One would think that as a long time patient on Doxil with such good results that Janssen would be interested in my outcome especially since I am taking the minimum dosage intensity and I am at high risk for serious side effects, if I were to discontinue using Doxil. One would think that I would be among the last patients to be deprived of the drug.

However, this issue is bigger than just its impact on me. This is a national if not an international crisis. There are many, many cancer patients affected by this tragedy that may not be as resourceful as me and have nowhere to turn. I have read some internet postings that have been heartbreaking. In my opinion, this is a form of attempted murder and now that there have been reported deaths in some cases, a form of murder.

I am questioning the specific reasons for the shortage. What role did the government play? What is the manner and method of this decision-making regarding who receives the drug? Who made the decision to withdraw the medication, was it the government, the manufacturer or was it the hospital? What criteria were utilized in the decision-making process? Were financial considerations involved?

Once I resolve the necessary steps to secure my next treatment, I plan to make it my personal mission to help increase awareness about this tragedy.

Dan Schiavello

DOXIL SHORTAGE QUESTIONS

1. When did J&J first learn of the pending shortage? Why did they never formally inform patients of the shortage?

2. Why did J&J first report that the Doxil shortage was due to unplanned downtime due to equipment failures knowing that the manufacturing suspension was voluntary and due to an internal review of documentation?

3. When was the last batch of Doxil manufactured? When will Doxil production be resumed?

4. How much Doxil has been stockpiled, where is it located and who is going to receive it?

5. What is the J&J transition plan claimed in the September 23, 2011 letter and who is the alternate supplier mentioned in the letter?

6. Why did J&J claim on 6/29/2011 that the shortage only affected New Patients and then announced the DOXIL Cares program for existing patients on 8/5/2011?

7. Why didn't J&J indicate a sense of urgency to doctors and/or the patients for registration of existing patients in the Doxil Cares Program?

8. Why didn't not inform patients so that they could advocate on their own behalf?

9. Why has there been a lack of transparency regarding production facilities, production rates, inventory, manufacturing transition plan and future resolution regarding the Doxil shortage

10. Why did J&J violate HIPAA by collecting patient information without consent, by not informing patients of their status on the waitlist, and by preventing cancer patients from making life or death decisions regarding their health?

11. Why wasn't there any medical necessity considered included in the Doxil Cares Program making it impossible for oncologists to practice good medicine?

12. J&J indicated that they are singularly focused on bringing Doxil back to patients, so what specific steps are being taken?

13. J&J indicated that are ultimately accountable and take full responsibility for the shortage and its ultimate resolution. What is specifically being done to help patients find Doxil or an alternative and to offset costs associated with grey market drug purchases, second opinions, travel and other costs associated with the impact of the shortage?

14. What role did the FDA play in the Doxil shortage? Why was there not an FDA consent decree issued considering Doxil is a life saving drug?

Susan G. Komen for the Cure®
Statement for the Senate Committee on Finance

"Drug Shortages: Why They Happen and What They Mean"
December 7, 2011

Thank you Chairman Baucus, Ranking Member Hatch, and distinguished Members of the Committee, for holding a hearing to highlight the critical problem of drug shortages and to receive input from health care and policy experts on ways to address this crisis.

On behalf of breast cancer survivors, their loved ones, and those who will fight the disease in the future, Susan G. Komen for the Cure® (Komen) appreciates this opportunity to comment on this important issue. Komen is the largest grassroots network of breast cancer survivors and advocates. At the heart of Komen's mission is saving lives, empowering people, ensuring quality care, and energizing science to find the cures. Since 1982, Komen has played a critical role in every major advance in the fight against breast cancer. With 230,480 new cases of invasive breast cancer expected to occur this year alone, we have grave concerns that, if left unaddressed, the drug shortages crisis will continue to deepen and eventually will have a serious impact on women who are currently being treated for breast cancer and those who will be treated in the future.

As most experts agree, drug shortages are a complex problem with no single, distinct root cause. While we work toward a comprehensive solution, Komen would like to express the breast cancer patient perspective and the essential elements of a solution that would address the needs of this population.

The economic forces and regulatory issues that have led to the number of drug shortages tripling annually since 2005 can only be addressed with a multi-faceted solution. As we actively seek legislative proposals and regulatory solutions to ensure access to lifesaving medicines while safeguarding their quality and safety, Komen urges legislators, drug manufacturers, and regulators to continue to keep the needs and interests of the patients who depend on these drugs as the focal point of any solution. After all, while many health care sector stakeholders are impacted, it is the patients who are most at risk when they are left unable to finish a treatment cycle, or are prescribed a drug regimen that was not their physicians' first choice for their unique needs. In some cases, the shortages are leading to dosing errors with grave consequences for patients. Additionally, both the government and patients must shoulder the cost of more expensive alternatives and the labor and time it takes to indentify substitute treatments, if they do exist.

We urge Congress to explore a combination of regulatory reform, possible incentives, and other measures to bring more manufacturing capacity online to ensure a stable supply of these critical drugs. Other regulatory proposals to consider include: helping manufacturers get additional supplies of Active Pharmaceutical Ingredients (APIs) certified; applying regulatory discretion when possible to efficiently resolve manufacturing problems; and expediting the FDA approval process by systematically reviewing and prioritizing applications waiting for approval that are relevant to drugs frequently susceptible to shortages. Any regulatory reform must be implemented in a manner that ensures high quality through oversight, while also mitigating the impact of any enhanced regulation that could lead manufacturers to take a product off the market rather than investing the money necessary to achieve compliance. In order to effectively exercise regulatory flexibility to proactively respond to drug shortages, FDA should systematically maintain and analyze data on drug shortages and their causes. Additionally, FDA needs to develop measures to adequately monitor this data.

Finding a comprehensive proposal may require exploring new incentives to develop greater capacity by bringing new manufacturers into the market and to encourage existing manufacturers to continue to produce the low cost, vital drugs that are vulnerable to shortages. A comprehensive review of the Average Sales Price (ASP) reimbursement formula and alternatives such as Wholesale Average Cost (WAC), should also be undertaken. We understand that while a drug's ASP is reported quarterly, in effect, CMS updates the ASP payments approximately every six months. This allows for minimal opportunities to adjust pricing, hindering flexibility to respond to market changes and to support production of shortage-prone drugs. While addressing the drug shortage problem may involve potential changes in the way that drugs are reimbursed by Medicare and private payers, any proposal must be developed in a manner that assures that incentives are not lost along the supply chain, and that the incentives actually facilitate bringing new supply sources and manufacturing capacity online. Executive agencies, Congress, and industry will have to work together to achieve the delicate balances needed to ensure that new policies do not result in unforeseen adverse consequences.

It is widely acknowledged that the gray market is a symptom rather than a cause of drug shortages, and that it exacerbates the problem. The safety concerns associated with turning to the gray market as an alternate source for drugs must be recognized. Congress should consider enacting laws to severely penalize price gouging by individual actors and companies. Existing laws designed to prevent abuses should be aggressively enforced and prioritized. Finally, a mechanism to report information about suspected hoarding, price gouging, and counterfeit drugs should be developed to augment investigation by law enforcement authorities.

While a comprehensive solution is being developed, communication surrounding existing or emerging drug shortages is critical. The necessary communication includes, but also goes beyond, what is included in current legislative proposals that require FDA notification of expected drug shortages by manufacturers. The FDA should explore ways to receive notification from and engage in communication regarding drug shortages with the whole supply chain and to develop and monitor data and trend information that would allow the agency to better predict potential shortages. It is critical to provide accurate and timely information about existing and expected shortages, and their potential duration, to physicians and other health care professionals who prescribe and administer drugs vulnerable to shortages, and to clinical trial investigators, to

the fullest extent allowed by confidentiality requirements. This way, health care practitioners and clinicians can proactively address an oncoming shortage by developing a plan to mitigate its impact on patients or to find alternative drugs before they are in a crisis situation.

Fifteen of the twenty-two cancer agents on the drug shortage list are needed for clinical research purposes. The significance of the impact on cancer research is due to the fact that cancer clinical trials rarely use placebos, and instead, test the standard of care treatment against or alongside the new treatment being investigated. As a result, groundbreaking clinical trials of cancer drugs are delayed or even halted by shortages that impact the standard of care cancer agents. This wastes research dollars, the time and resources directed toward the trials, and the personal investment made by investigators and participating patients who have courageously agreed to enroll in these trials. Treatment delays and obstacles to research efforts being translated into approved anti-cancer drugs affect patients' chances of survival.

It is also critical that physicians are promptly notified of all actual and likely shortages, so that they can fulfill their professional obligation to discuss the implications of shortages on treatment regimens and to advise patients of treatment options and risks. If the preferred treatment protocol needs to be adjusted because of a possible or existing shortage, patients should be informed of any possible ramifications of interruptions or delays and the consequences and side effects associated with substitute treatments. They should also be given the choice to inquire about and discuss other options. After all, we must keep in mind, that while the whole health care system is impacted, it is these patients' lives that are at risk.

Thank you for this opportunity to submit this statement on an issue of such vital importance to cancer patients and those who love them. On behalf of Susan G. Komen for the Cure, I appreciate the efforts Congress is making to develop and implement a comprehensive solution to resolve a crisis that is jeopardizing patient access to treatments that save lives.

If you have any questions or would like any additional information, please do not hesitate to contact me or Karen Handel, Senior Vice President, Public Policy, Komen Advocacy Alliance, at 202.654.6536 or khandel@komen.org.

Sincerely,

Elizabeth Thompson
President
Susan G. Komen for the Cure®

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