

**REVIEW OF THE PROPOSED GENERIC DRUG AND
BIOSIMILARS USER FEES AND FURTHER EXAM-
INATION OF DRUG SHORTAGES**

HEARING
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES
ONE HUNDRED TWELFTH CONGRESS

SECOND SESSION

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¹Ms. Mullin, Mr. Beckerman, and Ms. Jensen did not present statements for the record.

**REVIEW OF THE PROPOSED GENERIC DRUG
AND BIOSIMILARS USER FEES AND FUR-
THER EXAMINATION OF DRUG SHORTAGES**

THURSDAY, FEBRUARY 9, 2012

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

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2123 of the Rayburn House Office Building, Hon. Joe Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Murphy, Gingrey, Latta, Lance, Cassidy, Pallone, Dingell, Towns, Engel, Capps, DeGette, and Waxman (ex officio).

Staff present: Clay Alspach, Counsel, Health; Michael Beckerman, Deputy Staff Director; Nancy Dunlap, Health Fellow; Paul Edattel, Professional Staff Member, Health; Debbie Keller, Press Secretary; Ryan Long, Chief Counsel, Health; Carly McWilliams, Legislative Clerk; John O'Shea, Senior Health Policy Advisor; Chris Sarley, Policy Coordinator, Environment and Economy; Heidi Stirrup, Health Policy Coordinator; Phil Barnett, Democratic Staff Director; Alli Corr, Democratic Policy Analyst; Eric Flamm, FDA Detailee; Karen Nelson, Democratic Deputy Committee Staff Director for Health; Rachel Sher, Democratic Senior Counsel; and Elizabeth Letter, Democratic Assistant Press Secretary.

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

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

Today, we will discuss two new user fee authorizations, one for generics and one for biosimilars, and also examine the worsening drug shortage problem facing our country. Under the terms of the Generic Drug User Fee agreement that industry and FDA have negotiated, industry will pay approximately \$1.5 billion over the next 5 years in exchange for more efficient and predictable review of generic drug applications and increased inspections of drug facilities.

Currently, there are approximately 3,000 generic drug applications sitting in a backlog at FDA. One of the goals of the agreement is to eliminate this backlog within 5 years, speeding generic drugs to the patients who need them without sacrificing quality or

safety. Another goal of the agreement is to have FDA inspect all drug facilities at an increased frequency and to bring parity between inspections of foreign and domestic facilities.

Industry and FDA have also negotiated a second user fee agreement for biosimilars—those products approved under the abbreviated approval pathway for biological products shown to be highly similar to an FDA-licensed biological product. This subcommittee has spent a great deal of time in the last few years trying to achieve a pathway to approval for biosimilars. This agreement authorizes four types of fees: application, product, establishment, and biosimilars product development, to make this a reality.

Finally, every day we are hearing from providers in our districts about increased difficulties in acquiring the drugs necessary to treat their patients. As this subcommittee looks to develop a package of ways to alleviate drug shortages, I look forward to hearing from our witnesses and learning their views on the matter.

Again, thank you to all of our witnesses on both panels and I will yield the balance of my time to Mr. Murphy from Pennsylvania for an opening statement.

[The prepared statement of Mr. Pitts follows:]

Rep. Joseph R. Pitts
Opening Statement
Energy and Commerce Subcommittee on Health
Hearing on “Review of the Proposed Generic Drug and Biosimilars User Fees
and Further Examination of Drug Shortages”
February 9, 2012

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OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. Thank you, Mr. Chairman.

Brand name and generic medicines are simultaneously necessary and essential components of quality and cost-effective healthcare, but approximately 78 percent of prescriptions dispensed in the United States in 2010 were filled with generic drugs. It is estimated that over the last 10 years, the use of generic medications has saved our healthcare system nearly \$1 trillion. However, in recent years, the backlog of generic drug applications at the Food and Drug Administration has dramatically increased. Today, there are over 2,500 applications awaiting review with an average review time of almost 31 months. At the same time, events like the 2007 contamination of heparin manufactured in China have raised serious concerns about the security of the U.S. pharmaceutical supply chain.

Today, 40 percent of all drugs sold in the U.S. are manufactured overseas and as much as 80 percent of the active pharmaceutical ingredients—called API—in those drugs come from foreign sources. According to the Government Accountability Office, FDA inspects U.S. pharmaceutical factories every 2 to 3 years but inspects overseas facilities on average only once every 9 years.

In the face of these challenges, the FDA and the generic pharmaceutical industry have come together with other stakeholders to negotiate a historic 5-year agreement that will bring less expensive therapies to market faster. Less expensive drugs mean better access to care for patients; that means fewer costly complications from untreated chronic diseases, fewer hospitalizations. Industry has agreed to do their part by paying \$1.5 billion in user fees to FDA over 5 years and in return FDA has pledged to review 90 percent of new applications within 10 months by year 5 of the agreement. The FDA has also agreed to work to address supply chain safety concerns while ensuring level playing fields for domestic and foreign manufacturers by achieving parity between domestic and foreign facility inspections.

Yesterday, I introduced the Generic Drug and Biosimilar User Fee Act of 2012 based on this agreement with Representatives Pallone, Pitts, and Waxman. I look forward to working with my colleagues on this committee as we review to enact this critical piece of legislation.

Finally, let me thank and commend Representative Dingell for his many years of leadership and work on the issue of drug safety. When we enact this legislation, it will be to a large extent because of his dedication and long-term efforts.

And with that, I yield back.

Mr. PITTS. The Chair thanks the gentleman and now yields to the ranking member of the full committee, Mr. Waxman, for 5 minutes for an opening statement.

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

Mr. WAXMAN. Thank you very much, Mr. Chairman.

Today, we begin the process of establishing two critically important programs at FDA that will help speed low-cost generic drugs and biosimilars to the market. Because these are new user fee programs that will now join the other long-existing programs, just yesterday, Representative Murphy, Pallone, Pitts, and I introduced the Generic Drug and Biosimilars User Fee Act which will give FDA the authority and resources it needs to review generic applications in a timely and effective manner. I am proud that we were able to work together in such a strong bipartisan fashion on this legislation. It reflects our shared commitment to ensuring that American patients have access to these life-saving medicines early and at a price they can afford.

I also want to commend FDA and the biotech and generic drug industries for the hard work they put into negotiating these thoughtful and thorough proposals. These programs are long overdue. We have had a long history of success with the other user fee programs for brand name drugs and medical devices. In contrast, for some time now, FDA's generic drug review program has been starved for resources, which resulted in a dramatic backlog of applications. That, of course, has meant fewer generic drugs on the market and consequently higher medication prices for American patients. At long last, this legislation will help us turn this untenable situation around.

Likewise, FDA will also now have the resources it needs to review applications for biosimilar drugs. By most accounts, biotech drugs are the most promising medicines on the horizon. This law will permit FDA to fully implement the newly established biosimilars pathway and we will all begin to see its benefits.

On a different note, I am encouraged that the subcommittee is taking another look at the very dire situation surrounding drug shortages. This is the kind of issue that can and should be tackled on a bipartisan basis. It is a complex and multifaceted problem but I feel confident that we will work together to find workable solutions.

Thank you for holding this hearing today and I look forward to the testimony of our witnesses. I yield back my time.

Mr. PITTS. The Chair thanks the gentleman and at this point recognizes the vice chairman of the Health Subcommittee, Dr. Burgess, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman, for the recognition.

Dr. Woodcock, welcome to our committee. Certainly, you have always been very receptive to our questions and we appreciate the efforts that you provided to me and my staff on our visit to the FDA a few months ago.

We are discussing two of the pending user fee agreements before the committee, but also today, I think many of us are interested in the issue of the drug shortages. When doctors lack the essential tools, they are extremely restricted as to what they can do for patients. It is a complex issue. You have stated that before. Your agency has stated that before. But make no mistake; the FDA has a role in helping us find a solution.

In calendar year 2010, over 240 drugs were identified as being in short supply or unavailable and more than 400 generic equivalents were backordered. Many generic lines operate at margins that are so tight that when production becomes difficult, they can't afford to make the changes to revamp their machinery and make those compounds available. In an ideal free market, competitors would then move in and assume this market share, but now we are in a situation where some competitors cannot afford to ramp up to meet the resulting demand. We have to ask ourselves is this the result of hyper-competition? And if so, is that ultimately a good thing? So is approval of multiple competitors in a limited space leading to market forces that actually end up driving patients back to branded products at higher prices and increased spending? Is that good in the long run?

And inevitably, we have to face the over 3,000 number of backlogs of generic applications and I am very interested in tracking the goals in this user fee agreement in regard to the one-time fee the industry has agreed to in order to clear that backlog.

Finally, we have to look at the issue of bioequivalence and when the Food and Drug Administration chooses to exercise the flexibility they have in the approval process. In some instances, I believe this authority has been used questionably. In others, I question why it hasn't been used at all. On January 6, in response to a request for flexibility on bioequivalent studies for a substitute for Doxil, a chemotherapeutic agent used in treating gynecologic cancer, Mr. Conner, the Director of Bioequivalence of the Office of Generic Drugs wrote, "the Food and Drug Administration may take steps to expedite regulatory reviews. However, the Agency has determined that it is necessary that bioequivalence or bioavailability study in patients be conducted."

Now, I don't have any other information on the quality of this submission, but I do know this: Doxil is gone now to treat patients. The line is shut down. Any stockpile that was there went to treat the ill, and that is appropriate, but how do you conduct a bioequivalent study if you don't have the product against which to test? When you are doing a randomized clinical trial, it requires that you have the product to test. You can't do that, and yet the Food and Drug Administration just simply wants to say, "Well, you have got to do the bioequivalence study." They are not telling us what we should do in this event where we have no product left against which to test. These are tools on which physicians rely every day, and what do we do when they are not there?

Here are some other observations: "A 51-year-old patient with platinum-resistant ovarian cancer had already been treated with another chemotherapeutic agent. She has few choices for therapy and would likely die before the drug shortage is corrected. I have three promising clinical trials which are now on hold because of shortages. Please help us." Another quote: "I cannot obtain Doxil for patients stabilized on therapy. I have switched to alternate drugs with more side effects." Another quote: "We have encountered regimen changes, difficulties with patient insurance approval, and an increase in hospitalization due to side effects of older regimens." I have 35 such testimonials as part of a survey conducted

by the Society of Gynecologic Oncology and the FDA letter, and I would ask that those be submitted for the record.

Look, no physician wants to tell a patient that they cannot receive the care they need because there is no treatment but because the product is simply not available and we won't provide alternatives is no solution at all.

I will be glad to yield the remaining time to anyone one on my side who would request it. If not, I yield back to the chairman.

Mr. PIRTS. Without objection, those will be entered into the record.

[The information follows:]



**Executive Summary of SGO's Drug Shortage Survey
September, 2011**

I. Overview

In July 2011, Janssen Products, LP announced the nationwide shortage of its product, doxorubicin HCl (Doxil) liposome injection – a common chemotherapy drug administered to patients with ovarian cancer. The Doxil shortage is one of more than 198 reported drug shortages as of August 25, 2011. According to the University of Utah Drug Information Service, there were 211 reported drug shortages for calendar year 2010. If current trends continue, it is estimated that more than 300 drugs will be in short supply by the end of 2011, an increase of approximately one-third. These shortages continue to cripple the country's healthcare system and physicians' ability to properly treat patients. It is also having a negative impact on current and future cancer clinical trials.

As a part of SGO's ongoing advocacy efforts to encourage appropriate access to care, data regarding the impact of these drug shortages was collected from our members' practice/institutions. SGO members were asked to share personal anecdotes that articulate the impact the drug shortage has had on their practice and patients. The information garnered from the survey will be used in SGO's messaging and grassroots efforts as well as in our work with fellow professional organizations and advocacy groups.

Background

The matter of medication supply shortages in this country continues to be a growing concern - one that has received an increasing level of interest in the media and from the Food and Drug Administration and the National Cancer Institute. It is estimated that an average of 150 new shortages occur annually, putting patients at serious risk -- especially those battling cancer. As part of its advocacy and public policy efforts, SGO, along with members in the National Coalition for Cancer Research (including ASCO), is supporting two bills that address the issue of FDA notification by a company of an impending drug shortage.

II. Methodology

On Wednesday September 7, 2011, SGO launched a nine-question survey via the online surveying tool, Zoomerang, to all members in an effort to gauge how the national drug shortage has affected their ability to treat patients with gynecologic malignancies. The survey was available for a week, officially closing on Thursday, September 15, 2011. In an effort to increase members' engagement in the survey, SGO's Corporate Communications department distributed

various articles on the drug shortage and published weekly reminders within the Society's bi-weekly newsletter *SGO Issues*.

The survey was sent electronically to all of SGO's 1,458 members for input and additional feedback. The survey was viewed by 124 members or eight percent of SGO membership.

Of those members:

- 101 members completed the survey (7%)
- 22 members clicked on the link and chose not to participate in the survey

III. Results

Below are the responses to the nine-question survey. Additionally, a summary of the open-ended comments made by 35 of the survey respondents is listed. (An Excel sheet of the results in Zoomerang is also attached)

1. Have you experienced a shortage and/or delay in obtaining the supply of chemotherapy drugs in your practice?

- **Yes – 98% (94 members)**
- No – 2% (2 members)

2. How long was the delay?

- A day – 1% (1 member)
- Less than a week – 5% (5 members)
- One to two weeks – 4% (4 members)
- More than two weeks – 13% (12 members)
- **A month or more – 77% (73 members)**

3. Approximately how many of your patients have experienced a delay/disruption of treatment as a result of the drug shortage?

- **Less than 10 – 43% (41 members)**
- 10- 20 – 41% (39 members)
- 20-30 – 13% (12 members)
- More than 30 – 3% (3 members)

4. How long have your patients experienced a delay/disruption of treatment?

- A day – 0%
- Less than a week – 5% (5 members)
- A week – 4% (4 members)
- Two weeks – 9% (8 members)
- More than two weeks – 18% (17 members)
- **Continuing, have suspended treatment – 64% (60 members)**

5. Was there an alternative drug available?

- **Yes – 63% (60 members)**
- No – 37% (35 members)

6. If No, please explain what course of treatment/options you selected?

- Suspended treatment for a week – 7% (3 members)
- Suspended treatment for two weeks – 16% (7 members)
- Suspended treatment indefinitely – 33% (15 members)
- **Other – 44% (20 members)**

7. Have the drug shortages impacted your ability to foster patient participation in clinical trials? If yes, how many?

- **1-2 – 51% (28 members)**
- 3-6 – 33% (18 members)
- 7-10 – 9% (5 members)
- 10 or more patients- 7% (4 members)

8. Do you or your institution anticipate any future shortages of additional drugs in the next six months?

- **Yes – 85% (81 members)**
- No – 15% (14 members)

9. Please share any specific stories regarding the shortage and its effects on your ability to treat your patients. (Verbatim comments listed below)

- We haven't had Doxil in ages and this is devastating as it is the best 2nd line agent. Had to switch to other agents. Very difficult for our patients as they travel hours to get to our University practice and many of the other second line drugs are weekly. For patients off trial, we can sub docetaxel for paclitaxel but have had colossal problems with neutropenia and treatment delays. Also have had to suspend enrolment on multiple clinical trials as we have no guarantee for paclitaxel. HUGE issue for both GOG and investigator initiated trials.
- Had to delay initiating a patient upon Doxil indefinitely.
- Had to delay treatment, skip a treatment or reduce dose because "pharmacy did not have enough".
- I have patients calling around the country for drug supply of Doxil. One patient flew to Toronto for a treatment and also brought vials back for next months' treatment in hopes of having home care administer.
- I had 20+ patients on Doxil and had to either suspend therapy or change drugs. Very disruptive to patient care.
- Doxil shortage disrupted many patients' treatments. Many who were responding to Doxil had to be switched to another drug that hasn't worked as well.
- Shortages of both paclitaxel and Doxil have adversely impacted our practice.

- Patients are receiving multiple cycles of adriamycin with more nausea and myelosuppression, as well as potential cardiac toxicity. We are unable to enroll on 252. We have industry trial using weekly paclitaxel on which we cannot enroll. We have changed therapy on at least 5 patients when they were having clinical responses to Doxil or paclitaxel.
- Patients can't get Doxil even though it was working well.
- Stopped enrolling in clinical trials requiring Doxil, substituted docetaxel on trials (even though data to do so is limited-- endometrial cancer pts, pt with h/o prior XRT).
- The drug Doxil, which is a well-tolerated and very commonly used drug for women with recurrent ovarian cancer, abruptly became unavailable. There is no equivalent (from a side effect point of view) alternative, and patients have been put on hold until the drug becomes available, while they are closely monitored for progression. Since one of our major trials requires progression on or after Doxil as an entry criteria, patients hoping to go on this trial as an alternative may find the study is closed by the time they have had a chance to try Doxil. The sudden lack of availability of Doxil has caused much anxiety for the women affected. Many have heard that production was stopped by the FDA despite lack of safety concerns, and they are quite distressed that the system has failed them so (I do not know if the rumors are correct). The lack of clear explanation as to what happened to so dramatically affect the supply of this drug manufactured at only one plant in the US, the lack of information as to when the drug will again be available, as well as the fact that some drug has apparently been released on a "first come first serve basis" without explanation as to how the limited supply was distributed have also been causes of concern.
- The shortage of Doxil limits enrollment on TRINOVA-2 and GOG9925
- I have had to delay treatment on several patients who were receiving Doxil salvage therapy who were responding to treatment- without good alternatives. I have been unable to accrue patients to a Doxil clinical trial or initiate Doxil salvage chemotherapy and have had to use more schedule intense regimens for patients with recurrent ovarian cancer.
- "I am retired so have no prescribing experience to pass on. However, I have had delays in delivery of personal prescriptions, none of which were rare, expensive or cancer-related. Is this a problem common to all drugs, not just cancer therapies?"
- Doxil is unavailable and I have had to change to topotecan in its place
- "I have had patients with metastatic endometrial and ovarian cancer for months that I have had to switch to other drugs because of lack availability of Doxil after failed attempts to get them drug thru the "Doxil Cares" program.
- 2-month delay on Doxil - POD in L groin.
- Higher expense of some drugs to the practice to substitute for the drugs not available.

- Have been approached by a drug company to sign an agreement to receive drug for patients if agree to not give more than 8 total cycles in a recurrent fashion for any patient who is already in treatment and to start no new patients on drug. Also the patient has to sign agreement to give company medical information. I have refused to sign any such agreement and have been told not to expect any drug in near future. Currently have 44 year old patient who has failed all other chemo but has had incredible response and stable disease while receiving drug (Doxil) both on clinical exam and marker assay with a ZERO performance status on drug. When have delayed treatment has rising titers but then responds when drug given. I think that there is ABSOLUTELY NO REASON that the drug company should have access to PHI of patients!
- Two patients on Doxil and one patient on carboplatin/taxol have had treatment suspension/delay more than three weeks.
- Two patients with significant response to Doxil now wait-listed and unable to obtain the drug. Both will have to switch from a working therapy to new treatment. This is very difficult because they don't necessarily qualify for clinical trials in the absence of progressive disease and with more meds given off trial, may prevent them from being candidates for trials in the future."
- "Cannot obtain Doxil for patients stabilized on therapy. Have switched to alternate drugs with more side effects. bleomycin, taxol and cisplatin shortages have come close to interrupting curative therapy for patients with breast and germ cell tumors. Our pharmacists spend at least 25% of the time now managing drug shortages throughout the hospital."
- Doxil shortage has required changing regimens for several patients and it has prohibited our ability to enroll these patients on in house clinical trials.
- I just had a patient this morning, doing well on Carbo/Doxil for recurrent ovarian CA, who we had to change to single-agent carbo because of no Doxil available. We are not starting anyone new on Doxil. I have a patient who I would like to refer to the PROCEED trial, but I do not know if they will take a new patient to lack of Doxil.
- We have had to develop an institutional policy whereby we declare whether a patient's chemotherapy is considered curative or not. If it is curative, the patient gets priority. If it is not, it is possible they may not receive drug.
- Patients moved to salvage regimens with increased toxicity due to lack of previously available regimens.
- Still waiting on Doxil.
- 18 patients on Doxil had to be switched to alternate treatment. Local hospitals having no taxol for inpatient treatment.
- Not knowing why there is a shortage is disconcerting to the patients and providers.

- "We have encountered regimen changes, difficulties with patient insurance approval with drugs not being on the approved formulary (i.e. Doxil) and an increase in hospitalizations due to side effects related to "older" regimens"
- Some of our patients have elected to halt therapy while awaiting drug availability.
- "Shortages in bleomycin delayed treatment start. Shortage in doxil required changing regimens. Very concerned about shortages in taxol, cisplatin and methotrexate."
- "I had a patient who was willing to travel to foreign country to receive treatment. Just before leaving she was informed that the drug, Doxil, was not going to be available in this foreign country. This patient will need a change in her treatment. I believe that her survival will be affected negatively. Another patient was will to give her Doxil to another patient. She was will to make the sacrifice so someone younger than her would be treated. She was will to sacrifice her life for another's. "
- "Patients and families concerned and upset, staff burdened with complex follow through"
- I have a 51 yo patient with platinum resistant ovarian cancer who has already been treated with topotecan. She has few choices for therapy and will likely die before the drug shortage is corrected! I have three promising clinical trials which are now on hold because of shortages of paclitaxel and pegylated liposomal doxorubicin. Please help us
- I have completed the drug shortage survey as requested. At Vanderbilt we have experienced some severe chemotherapy shortages but anticipation by our pharmacy staff and working together with the whole oncology group to prioritize treatment needs has mitigated any significant patient problems...thus far. I attach the most recent drug list which shows a great concern about Mesna at this point.

IV. Conclusion

Based on the high response rates to the questions asked above and survey participants open-ended comments; SGO members and their patients have clearly been affected by the national drug shortage. SGO members and health care providers across the country are concerned about their patients' survival rates and quality of life due to the lack of these medications.

SGO plans to use these results, along with members' personal stories to create a position statement on this issue. The Statement will then be shared with the SGO membership, affiliated advocacy groups, and national policymakers.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Azaya Therapeutics
Attention: Michael Dwyer
12500 Network Blvd.,
Suite 207
San Antonio, TX 78249

JAN 06 2012

Reference Number: OGD #11-0821

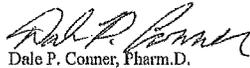
Dear Mr. Dwyer:

This letter is in response to your correspondence dated October 31, 2011. You inquired whether the Office of Generic Drugs (OGD) would consider granting a waiver of the *in vivo* and *in vitro* bioequivalence (BE) studies for your test product, Doxorubicin Hydrochloride Liposomal Injection, due to shortages of the reference product. The OGD has the following recommendations:

1. You state that for the past six months you have been unable to procure DOXIL[®] to conduct BE studies due to a shortage of this drug product on the market.
2. The agency has carefully evaluated the information provided regarding the shortage of the reference product, DOXIL[®] (Doxorubicin Hydrochloride Liposomal Injection), and has verified the shortage from official sources. The FDA continues to explore approaches to help prevent and mitigate shortages under existing statutory authorities. Consistent with the statutory responsibility to ensure the safety and effectiveness of the drug supply, the FDA may take steps to expedite the regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes, whenever it determines that expedited review would help to avoid or mitigate existing or potential drug shortages. The FDA may also exercise flexibility through regulatory discretion by working with manufacturers to identify means to mitigate the dangers of products with quality issues. However, the Agency has determined that it is necessary that a bioequivalence or bioavailability study in patients be conducted for this drug product in order to assess its safety and efficacy prior to approval. Therefore, your request for the waivers of *in vivo* and *in vitro* BE studies for your test product, Doxorubicin Hydrochloride Liposomal Injection, can not be granted at this time.

If you have any questions, please call Teresa Ramson, Pharm.D., Project Manager, Division of Bioequivalence at 240-276-8782. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Mr. PITTS. And the Chair now recognizes the ranking member of the Subcommittee on Health, Mr. Pallone, for 5 minutes for an opening statement.

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

Mr. PALLONE. Thank you, Chairman Pitts.

This hearing is the second in a series of important hearings that this subcommittee will hold in relation to the FDA User Fee Agreements, and I welcome everyone for joining us. And as I noted last week, I am encouraged by the bipartisan nature of these efforts, and I look forward to working with my colleagues.

Today's topics will cover two brand new user fee programs that the subcommittee will authorize. The first is a Generic Drug User Fee Agreement, also known as GDUFA. That will create a program at the FDA in order to help expedite review of their applications similar to the way brand name drug manufacturers pay user fees. Primarily, the agreement will help address the significant backlog of generic applications currently at the FDA. Unfortunately, over the last several years, this backlog has continued to grow at an alarming rate. In fact, the median time for a generic drug approval has doubled to 32 months, and that means all these generic drug products are kept off the market and out of the hands of consumers, which is a waste and simply too long.

Generic drugs, as we know, have proven to help lower healthcare costs. In the last decade alone, generic drugs have provided more than \$824 billion in savings to the Nation's healthcare system. Clearly, bringing generic drugs to market faster should be a priority, and luckily, the generic industry was able to recognize that we must provide the Office of Generic Drugs with adequate resources to do their job effectively. As much as I advocate for increased government funding for the FDA, that simply has become too difficult a battle to overcome, and so I appreciate the industry's ability to work with the FDA and move forward on a strong agreement and I commend your efforts.

The second user fee program is the Biosimilars User Fee Agreement, also known as BsUFA, which is the product of the Biologics Price Competition Innovation Act, the law that created a pathway for biogeneric medicine onto the marketplace. This agreement came together through a collection of brand and generic companies and FDA. Now, I know it is difficult for many to comment on the strength and robustness of the agreement because of the law's infancy, but it is a step forward in providing FDA the necessary resources to bring promising medicines to patients at a lower cost and I am supportive of its passage. I think that both Mr. Waxman and Mr. Murphy mentioned that last night, the two of us, as well as Chairman Pitts—the four of us I should say—introduced a standalone measure that covers both these agreements and shows that they have bipartisan support and that we are going to move forward with them.

Another issue under discussion today is the current drug shortage of vital medications that are impacting clinicians, hospitals, and patients who have depended upon these medications for years.

It is alarming the drugs that have been around for so long would suddenly be the most difficult to keep hospitals, pharmacies, and doctors' offices supplied with. I strongly believe this committee has the responsibility to address this sudden increase in drug shortages. We had a hearing last September that brought light to some important inadequacies of the system and I know there is a strong bipartisan appetite to work out a solution and I hope that we can get there. It is not a simple task but there are strong ideas that we have to consider and flesh out.

Lastly, Ms. DeGette has a bill that focuses on industry reporting as a worthy objective. I am also aware the generic industry has a proposal that we will be discussing today about a voluntary self-regulatory system. While I welcome their advocacy on addressing the problem, self-regulation always raises some critical questions. So I look forward to hearing more about that and I trust the FDA and our other witnesses can give specific insight into some of these proposals.

I wanted now to yield what time I have left to the chairman emeritus, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, as I have brought to the committee's attention in the past, drug supply chain safety is critical to the issue of health and safety to the American people. This hearing is going to reinforce how imperative it is to provide FDA with appropriate authorities and resources to secure our medicines. This committee has a long bipartisan history of working on this issue and looking into drug safety. It is now time for us to act. Our friends in the Senate have put together a bipartisan working group on this matter and we in the House should follow suit. Time is short. If we don't work together in good faith on this issue, we will not be finding a solution and the situation will continue deteriorating with death and hurt occurring throughout the American population by reason of our failure to address the difficulty. The American public deserves a solution.

As we proceed today, I am asking my colleagues to join me in working on this vital issue and to demonstrate to the American people that Congress does indeed work for them and that we follow on the steps that we took in the last Congress to see to it that we made foods much safer than they were by following on and addressing now questions relative to the safety of pharmaceuticals, appliances, and devices, and ultimately, cosmetics.

And I thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman. That concludes the opening statements for the members. We are now voting on the floor. So we have two votes. We will take a recess until the end of the second vote at which time we will reconvene.

The subcommittee stands in recess.

[Recess.]

Mr. PITTS. The subcommittee will come to order.

Our first panel will have just one witness, Dr. Janet Woodcock, the Director of the Center for Drug Evaluation and Research at

FDA. We are happy to have you with us today, Dr. Woodcock, and your written testimony will be made part of the record and you are recognized for 5 minutes to summarize.

STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY THERESA MULLIN, DIRECTOR, OFFICE OF PLANNING AND INFORMATICS, CENTER FOR DRUG EVALUATION AND RESEARCH; PETER BECKERMAN, SENIOR ADVISOR, OFFICE OF POLICY, FOOD AND DRUG ADMINISTRATION; AND VALERIE JENSEN, ASSOCIATE DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, DRUG SHORTAGE PROGRAM, FOOD AND DRUG ADMINISTRATION

Ms. WOODCOCK. Thank you very much and good morning.

Mr. Chairman and members of the subcommittee, I would really like to thank you for the opportunity to testify about three important issues: the United States Generic Drug Program and user fees that would support it, the new Biosimilars Program and proposed user fee, and the ongoing crisis of shortage of essential drugs in the United States.

I am joined today by Dr. Theresa Mullin on my right, who is the director of the Office of Planning and Informatics at the Center for Drugs. Dr. Mullin was the lead negotiator on Prescription Drug User Fee Program and on the Biosimilars Program. And to my left is Mr. Peter Beckerman, who is the senior advisor for policy in the Office of Policy at FDA. And he was one of the lead negotiators on the Generic Drug User Fee Program.

Since enacted by Congress in 1984, the current generic drug program has been a stunning success by most accounts. Today, over 3/4 of prescriptions dispensed are for high quality, affordable generics, as the members have said, saving Americans billions of dollars literally. But this program has been the victim of its unprecedented success. Applications to the program have skyrocketed and the program has not been able to keep up. Times to approval have lengthened and are prolonged, and over 2,000 applications are in a so-called backlog at the Office of Generic Drugs.

At the same time, globalization of the industry has challenged FDA to assure the same level of inspectional coverage that is carried out domestically for the foreign facilities. The new user fee program proposed to Congress addresses both these problems head on. The program would bring timelines and predictability to the review process, eliminate the backlogs. It would also provide a level playing field for inspections to ensure that the same quality standards are maintained wherever in the world the generic drug is made. These changes will ensure that U.S. consumers continue to have access to safe, effective, high quality, and affordable generic drugs.

The proposed Biosimilar User Fee Program is intended to support a new emerging industry. Biologics drugs developed over the past 20 years have provided new and effective treatment options for patients with serious diseases such as rheumatoid arthritis and cancer, but the generic drug program that existed did not apply to and was not really appropriate for these complex biological mol-

ecules. In 2007, Congress created a new pathway for biosimilar biologics and instructed FDA to develop a user fee proposal, which we have done. This program is intended to support an emerging industry and I will be very pleased to be able to discuss it.

I would like to thank the members—Mr. Murphy and Mr. Pitts and the additional members—for introducing legislation. We are really happy to hear that there is bipartisan support and we look forward to working with you.

I am also pleased to announce that, later today, FDA will introduce three draft guidances for industry on biosimilars. These contain technical information that will help the industry as they develop these new products for the U.S. market.

The third topic, drug shortages, is a very important issue. Millions of Americans rely on medicines to support or sustain their health, as we heard from Dr. Burgess. The recent shortages of sterile injectable drugs, many of which are essential in cancer treatment or in seriously ill patients, have brought a spotlight on this problem. The causes of drug shortage are multi-factorial, but in this case, a perfect storm came together to create the current situation of shortages. FDA does everything possible to both prevent and ameliorate shortages, including stimulating the production of other manufacturers, allowing risk mitigation strategies for products that have manufacturing difficulties, moving up the queue of applications so we could get additional products onto the market to alleviate shortages, and even arranging for temporary importation of similar products from other countries. For the current shortages, this has not been enough and hospitals and clinicians are facing and have been facing significant shortages.

We look forward to working with you to ensure that Americans have continued, uninterrupted access to effective, safe, high quality, and affordable drugs to sustain their health. Thank you very much.

[The prepared statement of Ms. Woodcock follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

**STATEMENT
OF
JANET WOODCOCK, M.D.
DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

BEFORE THE

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

**“REVIEW OF THE PROPOSED GENERIC DRUG AND BIOSIMILARS
USER FEES AND FURTHER EXAMINATION OF DRUG
SHORTAGES”**

February 9, 2012

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the negotiated recommendations for a generic drug user fee and a biosimilar user fee program, as well as to update you on actions the Agency is taking to address the ongoing problem of drug shortages.

The proposed user fee programs for generic drugs and biosimilars are modeled on the successful Prescription Drug User Fee Act (PDUFA) program which, over the past 20 years has ensured a more predictable, consistent, and streamlined premarket program for industry and helped speed access to new safe and effective prescription drugs for patients. Under a user fee program, industry agrees to pay fees to help fund a portion of FDA's drug review activities while FDA agrees to overall performance goals, such as reviewing a certain percentage of applications within a particular time frame. As a result of the continued investment of PDUFA resources, FDA has dramatically reduced the review time for new drugs, without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval. New legislation is needed to allow FDA to establish similar programs for generic drugs and biosimilar drug products.

Generic Drug User Fees

As a result of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as Hatch-Waxman Amendments passed by Congress more than a quarter of a century ago, America's generic drug industry has been developing, manufacturing, and marketing—and FDA has been reviewing and approving—lower-cost versions of brand-name drugs. This legislation and the industry it fostered has been a true public health success. Last year, approximately 78 percent of the more than 3 billion new and refilled prescriptions dispensed in the United States were filled with generics. In the last decade alone, generic drugs have provided more than \$931 billion in savings to the nation's health care system.

This success, however, also has come to represent a significant regulatory challenge, and delays in approvals of generic drugs have emerged as a major concern for the generics industry, FDA, consumers, and payers alike. Unlike the brand manufacturers who pay fees under PDUFA, the generic industry does not pay a user fee to support FDA activities related to its applications. Over the last several years, the time it takes for FDA to approve a generic drug has nearly doubled as FDA's resources have not kept pace with an increasing number of Abbreviated New Drug Applications (ANDA) and other submissions related to generic drugs. The number of generic drug submissions sent annually to FDA has grown rapidly, reaching another record high this year, including nearly 1,000 ANDAs. Drug Master Files² have grown at a comparable pace and have reached similar heights. The current backlog of applications pending review is estimated to be over 2,500. The current median time to

¹ "An Economic Analysis of Generic Drug Usage in the U.S." Independent Analysis by IMS Health, Sept. 2011 <http://gphaonline.org/sites/default/files/GPhA%20IMS%20Study%20WEB%20Sep20%2011.pdf>.

² Drug Master Files are widely used to provide FDA with information about the drug substance, also known as the active pharmaceutical ingredient (API).

approval is approximately 31 months, though it should be noted that this includes time the application is back with the sponsor to answer any questions FDA may have about the application.

The regulatory challenge of ensuring safe, high-quality generic drugs includes inspecting manufacturing facilities, where the challenge is not just one of numbers but also of geography. To keep pace with the growth of the generic drug industry, FDA has had to conduct more inspections as the number of facilities supporting those applications has also increased, with the greatest increase coming from foreign facilities. Currently, the number of foreign Finished Dosage Form (FDF)³ manufacturers exceeds the number found in the United States. The generic industry is also experiencing significant growth in India and China, a trend expected to continue. Foreign inspections represent a significant challenge and require significant resources.

The generic drug user fee agreement is designed to address the regulatory challenges mentioned above in an affordable manner. The annual fee total proposed represents approximately one half of 1 percent of generic drug sales. This modest cost should be offset by benefits received by the industry, as faster review times will bring products to market sooner.

³ An FDF is the final drug product (e.g. tablet, capsule). An FDF is made up of both API(s) and any inactive excipients.

Overview of the Proposed Generic Drug User Fee Program

To develop recommendations for a generic drug user fee effective beginning FY 2013, FDA conducted a process that involved the generic drug industry and public stakeholders. In addition to the negotiation sessions with industry trade associations, there were numerous public stakeholder meetings open to all, including industry, patient advocates, consumer advocates, health care professionals, and scientific and academic experts. The final agreement and the goals FDA and industry have agreed to were transmitted to Congress on January 13, 2012.

The Generic Drug User Fee Act (GDUFA) proposal, as negotiated, is aimed at putting FDA's generic drugs program on a firm financial footing and providing the additional resources necessary to ensure timely access to safe, high-quality, affordable generic drugs. The proposal focuses on quality, access, and transparency. Quality means ensuring that companies, foreign or domestic, that participate in the U.S. generic drug system are held to the same consistent high-quality standards and that their facilities are inspected biennially, using a risk-based approach, with foreign and domestic inspection frequency parity. Access means expediting the availability of low-cost, high-quality generic drugs by bringing greater predictability and timeliness to the review of ANDAs, amendments, and supplements. Transparency means requiring the identification of facilities involved in the manufacture of generic drugs and associated APIs, and improving FDA's communications and feedback with industry to expedite product access and enhance FDA's ability to protect Americans in our complex global supply environment.

The additional resources called for under the agreement will provide FDA with the ability to perform critical program functions that could not otherwise occur. With the adoption of user fees and the associated savings in development time, the overall expense of bringing a product to market is expected to decline. The program is expected to provide significant value to small companies and first-time entrants to the generic market. In particular, these companies will benefit significantly from the certainty associated with performance review metrics that offer the potential to dramatically reduce the time needed to commercialize a generic drug, when compared to pre-GDUFA review times.

In addition, the variety of funding sources for the program will ensure that participants in the generic drug industry, whether FDF manufacturers or API⁴ manufacturers, whether foreign or domestic, appropriately share the financial expense and benefits of the program. The broad range of funding sources, including and across facility and application types, as well as the large number of each, ensures that individual fees remain reasonable and significantly lower than associated branded drug fees.

Program Funding and Metrics

If enacted as negotiated, as noted above, the program would provide FDA with additional funding for all aspects of the generic drug program in the amount of \$299 million per year, for five years, adjusted annually for inflation. With those additional user fee funds, FDA agrees to undertake a series of immediate program enhancements and performance

⁴ An API is the drug substance responsible for the therapeutic effect (e.g. the chemical aspirin that is combined with excipients to produce the FDF aspirin tablet).

goals. Many performance metrics and efficiency enhancements are set forth in the negotiated documents. The proposed goals, which will, in most cases, be phased in, include:

1. New Applications: FDA will review and act on 90 percent of complete electronic ANDAs within 10 months after the date of submission;
2. Backlog: FDA will review and act on 90 percent of all ANDAs, ANDA amendments, and ANDA prior-approval supplements pending on October 1, 2012, by the end of FY 2017; and
3. Inspections: FDA will conduct risk-adjusted biennial Current Good Manufacturing Practice (CGMP) inspections of generic API and generic FDF manufacturers with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

Under the program, fees would derive from two primary sources: generic drug-related submissions and generic drug-related facilities. In the first year of the program, there would also be a fee assessed for applications that are pending on October 1, 2012, the so-called “backlog.” Like PDUFA, individual fee amounts would be set annually, with the total annual user fee revenue target specified in statute. Overall, 70 percent of the user fee revenue would be generated by facility fees and 30 percent by application submission and Drug Master File fees. In the first year that ratio will be slightly different because of the one-time backlog fee. The revenue from facilities is split, with 80 percent provided by the FDF manufacturers and 20 percent by API manufacturers, a ratio determined and recommended by the generics industry.

As in all of FDA’s other medical product user fee programs, under the proposed generic drug user fee program, user fee funding would supplement appropriated funding to

ensure sufficient resources for the Agency's generic drug review program, and guarantees are in place to ensure that the user fees are supplemental to annual appropriations in the budget.

Biosimilars User Fees

A successful biosimilars review program within FDA will spark the development of a new segment of the biotechnology industry in the United States. The Biologics Price Competition and Innovation Act (BPCI Act) of 2009, which was enacted as part of the Affordable Care Act of 2010, established a new abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. With this new abbreviated approval pathway, a biosimilar biologic can be approved by demonstrating, among other things, that it is highly similar to a reference biological product already licensed by FDA. Development of biosimilars is expected to be less risky, less costly, and take less time; therefore, approved biosimilars are expected to be less expensive than the reference product. This program will provide significant benefits for patients, making available more affordable treatments that clinicians will know are biosimilar or interchangeable. The development of this new market segment will expand the opportunities for technical innovation and job growth.

Background

A biosimilar is a biological product that is highly similar to a U.S.-licensed reference product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity, and potency of the product.

Under the transition provisions in the BPCI Act, user fees for a biosimilar biological product are assessed under PDUFA. Accordingly, currently, user fees for biological products are the same, regardless of whether the biologics license application (BLA) is submitted under the new, abbreviated biosimilar pathway or under the previously existing approval pathway for biological products. However, PDUFA IV expires on September 30, 2012, and the BPCI Act directs FDA to develop recommendations for a biosimilars user fee program for fiscal years 2013 through 2017. To develop these recommendations, FDA consulted with industry and public stakeholders, including patient advocates, consumer advocates, health care professionals, and scientific and academic experts, as directed by Congress. The final recommendations were transmitted to Congress on January 13, 2012.

Program Funding and Metrics

The proposed biosimilars user fee program for FY 2013 to 2017 addresses many of the top priorities identified by public and industry stakeholders and the most important challenges identified by FDA. The proposed biosimilars user fee program is similar to the PDUFA program in that it includes fees for marketing applications, manufacturing establishments, and products. However, there are some differences because of the nascent state of the biosimilars industry in the United States. For example, there are no currently marketed biosimilar biological products; accordingly, the recommended biosimilars user fee program includes fees for products in the development phase to generate fee revenue in the near-term and to enable sponsors to have meetings with FDA early in the development of biosimilar biological product candidates.

As in all of FDA's medical product user fee programs, the proposed biosimilars user fee program supplements appropriated funding to ensure sufficient resources for the Agency's review programs. Under the proposed biosimilars user fee program, FDA would be authorized to spend biosimilars user fees on Agency activities related to the review of submissions in connection with biosimilar biological product development, biosimilar biological product applications, and supplements. This would include activities related to biosimilar biological product development meetings and investigational new drug applications (INDs). It would also include development of the scientific, regulatory, and policy infrastructure necessary for review of biosimilar biological product applications, such as regulation and policy development, related to the review of biosimilar biological product applications, and development of standards for biological products subject to review and evaluation.

The biosimilars user fee program would support FDA activities at the application stage, such as review of advertising and labeling prior to approval of a biosimilar biological product application or supplement; review of required post-marketing studies and post-marketing studies that have been agreed to by sponsors as a condition of approval; the issuance of action letters that communicate decisions on biosimilar biological product applications; and inspection of biosimilar biological product establishments and other facilities undertaken as part of FDA's review of pending biosimilar biological product applications and supplements (but not inspections unrelated to the review of biosimilar biological product applications and supplements). Finally, it would support some activities at

the post-approval stage, such as post-marketing safety activities, with respect to biologics approved under biosimilar biological product applications or supplements.

Proposed Fees

The proposed biosimilars user fee program includes biosimilar product development, marketing application, establishment, and product fees. The initial and annual biosimilar product development fees for biosimilar biological products in development would be equal to 10 percent of the fee established for a human drug application under PDUFA for that fiscal year. The sponsor would pay biosimilar product development fees each year until the sponsor submits a marketing application for the product that is accepted for filing, or discontinues participation in the biosimilar product development program for the product. The proposed marketing application fee for a biosimilar biological product is equal to the fee established for a human drug application under PDUFA, minus the cumulative amount of any biosimilar product development fees paid for the product that is the subject of the application.

Finally, the proposed establishment and product fees are equal to the establishment and product fees under PDUFA for any fiscal year because the level of effort required for FDA oversight of manufacturing and post-marketing safety activities is expected to be comparable for biosimilars and biological products under PDUFA. FDA anticipates a modest level of funding from these sources, initially because only biosimilar biological products that are approved for marketing would be subject to these fees.

Proposed Performance Goals and Procedures

The proposed performance goals include new types of development-phase meetings with associated time frames for timely review of data and feedback. In addition, the proposed performance goals include application review, first-cycle review, proprietary name review, major dispute resolution, clinical holds, and special protocol assessment performance goals. The proposed application performance goals for biosimilars are similar to the PDUFA performance goals and include the following:

1. Review and act on original biosimilar biological product application submissions within 10 months of receipt. Performance targets phase-in starting from 70 percent in FY 2013 to 90 percent in FY 2017.
2. Review and act on resubmitted original biosimilar biological product applications within 6 months of receipt. Performance targets phase-in starting from 70 percent in FY 2013 to 90 percent in FY 2017.
3. Review and act on 90 percent of original supplements with clinical data within 10 months of receipt.
4. Review and act on 90 percent of resubmitted supplements with clinical data within six months of receipt.
5. Review and act on 90 percent of manufacturing supplements within six months of receipt.

Drug Shortages

In September of last year, Dr. Howard Koh, Assistant Secretary for Health at HHS, testified before this Subcommittee to discuss the growing problem of drug shortages. FDA and the Administration at large share your concern about the rising incidence of drug shortages in the United States and the significant and even life-threatening impact of these shortages on patients, and I am pleased to have the opportunity to update you on what FDA has been doing to help alleviate this problem. Although many of the root causes of drug shortages are beyond our control, we are committed to addressing this important issue and look forward to working with this Subcommittee on this issue.

Manufacturers can play a critical role in avoiding shortages by taking appropriate measures to reduce the risk of unplanned disruptions in supply. For example, manufacturers who maintain their facilities and equipment in good working order, develop contingency plans to minimize the effects of unanticipated problems, and work closely with FDA to resolve potential problems are less likely to face shortage situations. Manufacturers can also help to minimize drug shortages and decrease the impact of shortages by notifying FDA as early as possible of situations that might lead to a drug shortage.

When FDA learns of a potential shortage situation, we work directly with the affected manufacturer to help prevent the shortage or to minimize its effect on patients. This may include developing temporary workaround solutions to manufacturing or quality issues; consulting with the manufacturer to resolve the underlying problem; or helping the manufacturer find additional sources of raw materials. We also expedite the review of

submissions by the manufacturer that may alleviate the drug shortage while continuing to meet safety standards, which may include requests to extend the expiration date of products, make manufacturing changes to increase capacity, use a new raw material source, or change product specifications. FDA can also use our regulatory discretion for a manufacturer to continue marketing a medically necessary drug, if the manufacturer can develop a method to resolve a quality issue prior to the drug's administration. A recent example was potassium phosphate, which is a medically necessary injectable drug needed for intravenous nutrition in critically ill patients. The firm found glass particles in the vials, posing a significant safety concern. The manufacturer was able to provide data to FDA showing the particles could successfully be removed with a filter. FDA then exercised enforcement discretion for the drug to be shipped with a letter to notify health care professionals that the filter needed to be used with the drug. This resulted in the drug being available for patients in a safe manner while the firm addressed the particulate issue for future production.

In addition to working with the affected manufacturer, FDA also works with third parties to determine whether they can help avoid or minimize the shortage. For example, our Drug Shortage Staff frequently reaches out to alternate manufacturers who may be able to initiate or ramp-up production of the product at issue. We also expedite reviews of generic applications for products facing potential shortages. In certain situations, when a shortage cannot be resolved immediately, we will use our regulatory discretion for the temporary import of non-FDA-approved versions of critical drugs after ensuring there are no significant safety or efficacy risks for U.S. patients.

Although our work has enabled the Agency to successfully prevent more than 250 potential shortages since the beginning of 2010, drug shortages are on the rise. In response to this growing problem, the Administration has taken several actions to better understand and respond to drug shortages. On September 26, 2011, FDA hosted a public meeting to gain additional insight into the causes and impacts of drug shortages and possible strategies for preventing or mitigating drug shortages. Interested parties who attended included professional societies, patient advocates, industry, researchers, pharmacists, and other health care professionals. A docket has been opened in relation to the public workshop, where comments can be received from the public.

On October 31, 2011, the President issued an Executive Order,⁵ which directed FDA, as well as the Department of Justice, to take action to help further reduce and prevent drug shortages, protect consumers, and prevent inappropriate stockpiling and exorbitant pricing of prescription drugs in shortage situations. In an effort to encourage broader reporting of manufacturing discontinuances, the President's order directs FDA to use all appropriate administrative tools to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life-supporting or life-sustaining, or that prevent debilitating disease. The Executive Order also requires FDA to expand its current efforts to expedite review of new manufacturing sites, drug suppliers, and manufacturing changes to help prevent shortages. Under the President's Order, FDA is also directed to report to the Department of Justice situations in which secondary wholesalers or other market participants have responded to potential drug shortages by stockpiling

⁵ <http://www.whitehouse.gov/the-press-office/2011/10/31/we-can-t-wait-obama-administration-takes-action-reduce-prescription-drug>.

medications or pricing drugs exorbitantly, so that the Department of Justice can determine whether these actions are consistent with applicable law. Since the issuance of the Executive Order, FDA has successfully prevented 114 drug shortages.

On the same day the President signed the Executive Order, the Administration announced its support for bipartisan bills (S. 296 and H.R. 2245) that would require all prescription drug shortages to be reported to FDA and would give FDA new authority to enforce these requirements. The Administration also announced that FDA would provide additional staffing resources to enhance the Agency's ability to prevent and mitigate drug shortages. Additionally, FDA released a report entitled "A Review of FDA's Approach to Medical Product Shortages" on its role in monitoring, preventing, and mitigating drug shortages, which included recommendations to further reduce the impact of these shortages.

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

increased level of reporting by manufacturers of potential supply problems has continued into 2012.

Also, on December 19, 2011, FDA issued an Interim Final Rule (IFR) amending regulations relating to provisions of the Federal Food, Drug, and Cosmetic Act requiring manufacturers who are the sole source of certain drug products to notify FDA at least six months before discontinuance of manufacture of the products. The IFR modifies the term “discontinuance” to include both permanent and temporary disruptions in the manufacturing of a drug product and clarifies the term “sole manufacturer” to mean the only manufacturer currently supplying the U.S. market with the drug product. The broader reporting resulting from these changes will enable FDA to improve its collection and distribution of drug shortage information to physician and patient organizations and to work with manufacturers and other stakeholders to respond to potential drug shortages. We requested comments on the IFR to be submitted by February 17, 2012.

Since the Executive Order was issued, FDA has continued its work to help prevent or mitigate drug shortages in a number of ways, including:

- Doubling the number of staff in the Center to assist in coordination and response activities, as well as expediting actions (e.g., inspections) that would help to alleviate drug shortages;
- Meeting with various stakeholders to discuss shared opportunities to prevent and mitigate shortages, including the Generic Pharmaceutical Association, the

Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization, manufacturers, and wholesalers;

- Exploring options for improving our drug shortage database for the tracking of shortages, as well as utilizing the database to develop prediction models for drug shortages;
- Working with the Department of Justice, as directed in the Executive Order, regarding issues related to stockpiling and exorbitant pricing, including reports from pharmacists and other health care professionals in connection with drug shortages; and
- Continuing to prioritize review applications for products that are in shortage situations.

FDA is committed to doing everything in our authority to prevent and address drug shortages and looks forward to working with the Subcommittee on this important issue.

CONCLUSION

Human drug user fees have revolutionized the drug review process in the United States since they were adopted 20 years ago, allowing FDA to speed the application review process without compromising the Agency's high standards. Final recommendations for generic drug user fees and biosimilars user fees offer a strong example of what can be achieved when FDA, industry and other stakeholders work together on the same goal. User fees provide a critical way for leveraging appropriated dollars, ensuring that FDA has the

resources needed to conduct reviews in a timely fashion. The passage of a generic drug user fee and a new biosimilars user fee would allow FDA to build upon the success of PDUFA.

Drug shortages present a challenge that we must work collaboratively to solve. FDA has taken a number of important steps and will continue to work with industry, health care professionals, and patients to address this issue. We welcome the opportunity to discuss this important topic with you both today and moving forward.

Thank you for your contributions to the mission of FDA. I am happy to answer questions you may have.

Mr. PITTS. The Chair thanks the gentlelady and now begins the questioning and I will recognize myself for 5 minutes for that purpose.

Dr. Woodcock, how many applications are in the generic backlog at FDA?

Ms. WOODCOCK. We count what you might consider a backlog to have about 2,000 applications.

Mr. PITTS. Two thousand.

Ms. WOODCOCK. That includes some drugs that couldn't be approved now because the patents haven't expired on the innovators. You can send in your application beforehand and then you have to wait. But there are many in that backlog that could be approved if we had time to get to them or had the inspectional resources to do the inspection.

Mr. PITTS. And how will the Generic Drug User Agreement help clear out this backlog?

Ms. WOODCOCK. The agreement has several parts and one is specifically directed at the backlog. What we have recommended to Congress is that there be a one-time backlog fee paid at the start of the program of \$50 million. That would go toward us beginning to work on the backlog. One of the goals of the program that we would be held to is clearing up the backlog by the end of the 5-year user fee program. So by that time, we would be in steady state—applications in the door, applications out the door with predictability in that process and timelines. So we would expect with the backlog fee and our commitments and timelines that the backlog would be eliminated.

Mr. PITTS. Can you be a little more specific on what kind of generic drug applications are in this backlog and how will clearing this backlog save patients in our healthcare system money?

Ms. WOODCOCK. Most of the drugs in the backlog are additional copies of a drug where there is already a generic because we expedite the first generic out the door to try and get patients that initial savings so that additional copies of a generic have been shown to further lower the cost of the drug, the price due to competition. So this is important for lower cost drugs and also to have a robust supply. I think we are learning and we know from the shortage situation it is important to have multiple manufacturers of important drugs.

Mr. PITTS. Now, in your testimony you talk about FDA's efforts to expedite review of manufacturer submissions to help alleviate drug shortages, and currently, it takes FDA 31 months to review these submissions. Can you give us more background on what expedite means? On average, how long does it take to expedite those submissions that can help alleviate drug shortages?

Ms. WOODCOCK. I can't give you an exact number but we have a queue, and so everything is waiting and usually generic drugs are reviewed first in and they are reviewed first. So if you are the third in, you are reviewed third and so forth for fairness purposes. What we do if there is a shortage drug where that application might help ameliorate the shortage, we pull it out of the queue and review it as quickly as possible. So much of that 30 months can be gone. If the application is good, we can review that rapidly and get that drug on the market. So we have very few drugs waiting in the

queue that actually would address shortages. We have identified any of those drugs and we have expedited review of the applications.

Mr. PITTS. Now, how will the Biosimilars User Fee Program provide predictability and consistency regarding the review of biosimilars applications, and how will the Biosimilars User Fee Program help this burgeoning industry?

Ms. WOODCOCK. The Biosimilars User Fee Program will provide predictability of timelines and review and process to this industry similar to what the Prescription Drug User Fee does for innovator products. To some extent, the biosimilars program was modeled on the GDUFA program. However, it has a development piece in it to recognize the emerging nature of this industry and that development piece, they pay fees and they get a series of development meetings so we can give them extensive advice on how to develop their products. And then when the final application comes in, there are timelines and goals associated with those timelines. So FDA, in exchange for having this user fee program, will be expected to meet those timeliness goals on review.

Mr. PITTS. All right, thank you.

My time has expired. I will recognize the ranking member of the subcommittee, Mr. Pallone, for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Woodcock, we have heard these statistics about the drug production overseas that 40 percent of drugs and 80 percent of the active pharmaceutical ingredients come from abroad. That is my concern. As you know, Mr. Dingell, Ms. DeGette, myself, and Mr. Waxman have introduced the Drug Safety Enhancement Act that gives the FDA authorities and resource to address the problem of these ingredients and drugs from overseas. You mention in your testimony the challenge represented by foreign inspections, but my understanding is that current law requires FDA to inspect domestic drug facilities every 2 years but is silent with respect to foreign facilities. That seems to be an uneven playing field obviously, and I know resources are always going to be an issue, but I still think that the bifurcation doesn't make sense.

You know, so assuming you have unlimited resources, which of course is absurd, but assuming you have unlimited resources, do you agree that inspecting foreign and domestic facilities at the same frequency would make sense?

Ms. WOODCOCK. Yes, I believe that what we need to do is a risk-based approach, and some facilities in the United States and some facilities overseas may need very close FDA supervision because of the problems they are having. Other facilities may be on a different schedule based on the risks that they pose but I don't believe—

Mr. PALLONE. They are not based on whether they are domestic versus overseas?

Ms. WOODCOCK. That is exactly right.

Mr. PALLONE. Now, would you need new authority to permit you to do that, which, you know, to make sure that it is not different foreign versus domestic and to do the risk assessment? Would you need new authority for that?

Ms. WOODCOCK. We primarily lack the resources to perform this inspectional program and one of the principal goals of the new Ge-

neric Drug User Fee Program is to level that playing field of inspection. And one of the proposals there is that we conduct risk-based surveillance inspections around the world and achieve parity or a level playing field on—

Mr. PALLONE. So it is more a question of the resources than new authority then?

Ms. WOODCOCK. Yes, I believe that. Of course the law sort of sends a message that you are supposed to do the domestic every 2 years and is silent on the foreign, but from what we are doing, we are trying to ensure the quality of drugs for our patients, and where the drug is produced should not be taken into account.

Mr. PALLONE. Thank you. Now, would it be helpful to have additional resources to conduct more foreign inspections of brand facilities? I mean this isn't confined to just generic, correct?

Ms. WOODCOCK. We need to inspect all facilities producing drugs of any kind, including over-the-counter drugs and so on at the appropriate intensity for the risk that they bear.

Mr. PALLONE. OK. Now, what about the responsibility of U.S. companies? You know, for example, you know, we have the heparin situation illustrated the importance of raising expectations of pharmaceutical companies to be familiar with their own suppliers, you know, coming from abroad. Do you think that U.S. companies should have to be able to ensure that the products they sell meet U.S. requirements even though those ingredients are coming from abroad? Are there any new authorities that would help the FDA in making sure that companies meet those responsibilities?

Ms. WOODCOCK. Yes. As we have said repeatedly, we feel that our authorities at the border in particular are somewhat limited and there are additional authorities that have been discussed that would aid in keeping foreign products that don't meet our standards out of this country.

Mr. PALLONE. All right, let me just ask—I have a minute left—with regard to BsUFA and the BsUFA negotiations. Both you and the FDA Commissioner Hamburg gave assurances to the generic industry that the Biosimilar User Fee Program would receive 20 million in funding. Now, I understand we are talking about, you know, money that would be shifted around within the Agency. What steps are being taken to make sure that that happens?

Ms. WOODCOCK. Well, we have made a commitment. Dr. Mullin, who is here, we have been just discussing our time reporting and other tracking mechanisms. We keep very close track of how we spend both our BA money and our user fee money.

Mr. PALLONE. But is this something that you are going to move around within the Agency, is it going to be in the budget, or is it a new \$20 million that we have to come up with? I assumed it was within the Agency. That is what I am trying to find out.

Ms. WOODCOCK. Of course we would appreciate, you know, having resources to conduct this program. However, we do have \$1.8 million right now in appropriated dollars for the biosimilars program and we would make up the money. If we don't receive appropriated money, we would use BA funds that are existing within the Center for Drugs.

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

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

Mr. MURPHY. Thank you, Mr. Chairman, and thank you, doctor, for being here, appreciate your candid and informed comments on this.

Let me start off by asking—I want to make sure I understand FDA rules with regard to these medications. The Federal Food and Drug Cosmetic Act assumes that a drug is adulterated unless the methods used for manufacture of drug products conform to good manufacturing practice. Am I right that it works under that assumption?

Ms. WOODCOCK. That is correct.

Mr. MURPHY. Can you explain the role and importance of these good manufacturing practices in terms of helping to ensure the safety and integrity of FDA-approved products? Can you explain how that works?

Ms. WOODCOCK. Certainly. When drugs are produced in mass production in a factory, all right, there are many procedures. The modern term would be quality management, oK, to make sure that each time the drug is produced adequately and of adequate quality and that no errors have occurred. And it would be amazing if you go in a factory as we do all the time to see how many times something can go wrong. And so you must check and you must observe and you must test and you must improve and do all that. And those are embodied in regulations called the current good manufacturing practices regulations. And we also have international agreements on a lot of this, how it should look, that we have worked out through the International Conference on Harmonization.

Mr. MURPHY. So the assumption is unless you have actually seen what they do and given your seal of approval to that, we are assuming it has not met that standard. Is that a fair statement?

Ms. WOODCOCK. Well, we have set standards for what the quality management should be like, and also we review the drug, make sure the testing and so forth will control the drug adequately, but until we go in there, we don't know if they are actually following those procedures. And they may follow them at one time and then later slip from that and get into problems and not produce a quality drug.

Mr. MURPHY. Hence the importance of inspecting plants on a regular or a tighter basis and you sometimes do a surprise visit and they occur in a short period and show up again.

I know we have had hearings in the past where there is no such thing as a surprise visit to a foreign country and they know you are coming—

Ms. WOODCOCK. That is correct.

Mr. MURPHY [continuing]. And when you are going. So do these practices differ in the United States versus other countries then in terms of how medications are manufactured?

Ms. WOODCOCK. You mean by the manufacturers themselves?

Mr. MURPHY. Yes, by the manufacturers themselves.

Ms. WOODCOCK. Well, there is a wide range of capacity and functionality in different countries, all right. In the United States there has been a long history of FDA inspections and under-

standing of what the standards are. Nevertheless, I will point out over the past year or so we have had multiple recalls and some of the drug shortage problems are due to U.S. manufacturers who are not being able to manufacture their product. So it requires vigilance and continued attention to be able to manufacture these products right. That said, in other parts of the world, it is much more uneven. They may have extremely modern factories and be right on top of their game, and there may be many factories that may be substandard in many areas.

Mr. MURPHY. So given all that, what is preventing the FDA from updating good manufacturing practices right now that require companies to verify their suppliers are complying? And associated with that, do you think the bills before us here sufficiently address your concerns, and either way, will you be able to offer the recommendations or cleaning up these bills if you feel that is necessary?

Ms. WOODCOCK. Yes, well, we would be happy to work with you. I believe that the user fee bills are not about policy or regulation. They are about providing extra resources to perform activities. The regulations or law around drug safety and quality have not been really modified for a long time and are probably not totally congruent with modern understanding. So there has been discussion by this committee and others about are there additional standards that could be put into place that bolster and bring these up to modern understanding of what is needed.

For example, I am always surprised and I am sure most Americans would be to hear that we can't really—there is a presumption that anything that is being imported to our country, a drug, is OK. And we have to prove that there is something wrong with it rather than the opposite. Most other countries that is not the case.

Mr. MURPHY. I want to make sure I hear what you are saying. You are saying you have to prove something is wrong with the imported drug? So what you told me before is with companies here there, there is an assumption that it is adulterated unless they can prove they have gone through inspection. But you are saying when a foreign drug comes over, the assumption is everything is fine unless you prove otherwise?

Ms. WOODCOCK. Yes, that—

Mr. MURPHY. It is two different standards.

Ms. WOODCOCK. Now, I am not a lawyer, all right, but that is how I understand the legal framework is set up. So we have to look at that and prove some way that it is not adequate for entry into the United States.

Mr. MURPHY. I appreciate it. I think that would come as a shock to most Americans to understand that that is how things are going. Thank you so much.

Ms. WOODCOCK. And I would tell you that is not the case in other countries where they can hold things at the border if they even feel that they may not meet the standards.

Mr. MURPHY. Thank you.

I yield back. Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman from Michigan, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy.

Welcome, Dr. Woodcock. I am sponsor of H.R. 1483, which I hope this committee will give some strong consideration to. My questions today are going to require only yes or no answers due to the fact that I have so many. Starting, over 70 percent of prescriptions filled today are for generic drugs. Considering the fact that 40 percent of all drugs come from overseas and 80 percent of pharmaceutical ingredients are also from overseas, it is critical that we be able to protect American consumers by ensuring the safety of the drug supply chain. In order to do this, FDA must clearly have the proper authorities in place.

Dr. Woodcock, yes or no if you please. Does the Federal Food and Drug Cosmetic Act require FDA to complete GMP inspections of domestic drug manufacturers every 2 years? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Does the Federal Food Drug and Cosmetic Act require FDA to complete GMP inspections of foreign drug manufacturers on a comparable basis? Yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. Would you have the resources to do it if they did?

Ms. WOODCOCK. Not currently.

Mr. DINGELL. Is it accurate to say that current law is silent on the frequency with which FDA must inspect foreign facilities? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Does FDA generally meet the biennial inspection requirement for domestic drug facilities currently? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Is it true that FDA does not inspect foreign facilities at the same frequency as domestic facilities? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Is it true that a lack of financial and personnel resources are contributing to factors not for inspecting foreign drug facilities more frequently? Yes or no?

Ms. WOODCOCK. I am sorry. Could you repeat that a little more slowly?

Mr. DINGELL. I will give it again. Is it true that a lack of financial and personnel resources are contributing factors to not inspecting foreign drug facilities more frequently? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you agree that conducting inspections of domestic and foreign drug facilities at comparable frequency is as important to ensuring a level playing field for drug manufacturers? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Sometime the playing field gets slanted against United States manufacturers because of our inability to inspect foreign manufacturers and suppliers of different kinds, isn't that so?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Can our goal be achieved by using risk-based inspection systems? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you agree that a risk-based inspection schedule for domestic and foreign drug facilities based, for example, on the compliance history, time since last inspection, volume and type of product would allow FDA to better target their resources? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you agree that conducting comparable inspections of domestic and foreign facilities is important to public health? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Do you agree that FDA needs adequate resources, both financial and personnel, to conduct comparable inspections of domestic and foreign drug manufacturers? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Does the Prescription Drug User Fee Agreement currently provide resources for preapproval inspection? Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Does the Prescription Drug User Fee Agreement currently provide resources for any inspections beyond preapproval inspection? Yes or no?

Ms. WOODCOCK. No.

Mr. DINGELL. As you know, the Generic Drug User Fee Agreement provides additional resources for FDA to conduct GMP inspections of both domestic and foreign drug facilities. Now, does FDA need similar resources for inspections of facilities manufacturing innovator drugs? Yes or no?

Ms. WOODCOCK. Yes, we need similar resources.

Mr. DINGELL. Now, one obstacle for ensuring comparable inspections of domestic and foreign facilities is a lack of complete and accurate information that FDA has on generic drug manufacturing establishments. Will the Generic Drug User Fee Act help FDA to identify all domestic and foreign drug and active pharmaceutical ingredient facilities involved in the making of generic drugs through registration? Yes or no?

Ms. WOODCOCK. Yes, as proposed.

Mr. DINGELL. And I am assuming that that is a very badly needed authority at Food and Drug. Is that yes or no?

Ms. WOODCOCK. Absolutely.

Mr. DINGELL. Mr. Chairman, I have completed my business and with 9 seconds to spare. I yield back the balance of my time.

Mr. BURGESS. [Presiding] The Chair thanks the gentleman for his gracious—

Mr. DINGELL. Mr. Chairman, I ask unanimous consent that the record will include an analysis of H.R. 1483, the Drug Safety Enforcement Act of 2011, of which I am a sponsor. Thank you, Mr. Chairman.

Mr. BURGESS. Without objection, so ordered.

[The information follows:]

H.R. 1483, the Drug Safety Enhancement Act of 2011

Forty percent of pharmaceuticals and 80 percent of active pharmaceutical ingredients for the US market are now produced in foreign countries, often China and India. Such facilities often operate under lower standards than US manufacturers, creating safety risks and an uneven playing field.

The Drug Safety and Enhancement Act seeks to hold manufacturers responsible for the safety of pharmaceuticals manufactured in foreign countries for the US market and ensuring that the FDA provides oversight of foreign manufacturers equivalent to that exercised on domestic companies.

This bill will:

- **Require manufacturers to implement improved quality and safety standards, including stronger supply chain management**
- **Require manufacturers to notify FDA of counterfeits or safety concerns and to list country of origin of drugs and drug components**
- **Strengthen oversight of importers and customs brokers**
- **Give FDA needed authorities including mandatory recall authority, subpoena power, and clear extraterritorial jurisdiction.**
- **Strengthen criminal and civil penalties to better deter crime**
- **Increase FDA inspections of foreign manufacturing to put it on par with domestic facilities**
- **Create new funding mechanisms for FDA inspectional activities, so globalization doesn't create burden on US taxpayers**

Require all manufacturers to implement basic quality and safety standards, including stronger supply chain management

- Companies selling drugs in the US market must implement quality system to ensure the safety and integrity of their products, including drug ingredients manufactured by a contractor or supplier. Quality systems should include management responsibilities, quality responsibilities, risk management, and supply chain management.
- Companies must be able to document their supply chains, and demonstrate quality control
- Companies must perform on-site audits of suppliers before beginning to purchase product from that supplier, and must implement quality agreements with suppliers

Require manufacturers to notify FDA of concerns about counterfeits or manufacturing defects that put Americans at risk, and to list country of origin of drugs and drug components

- Companies must notify the FDA when use of or exposure to drug may result in illness or injury to humans or animals; significant loss or theft; reasonable probability that a drug has been or is being counterfeited; repeated failures by a component manufacturer to ensure compliance with quality systems; any incident causing a drug to be mistaken for, or its labeling applied to, another drug; and any contamination or significant chemical or physical change or deterioration after distribution, or any failure of a distributed lot to meet established specifications.

- Require manufacturers of finished drug products to list on their websites the countries of origin for their finished drugs as and the active ingredients in those drugs.

Strengthen oversight of importers and customs brokers

- Require importers and customs brokers to register with the FDA, and permit FDA to require additional documentation at importation. Create an importer registration fee to support oversight activities
- Require the Secretary to create good importer practice regulations

Give FDA needed authorities including mandatory recall authority, subpoena power, and clear extraterritorial jurisdiction.

- Give FDA the power to order a drug recall, allowing for an industry appeals process (as exists for food and medical devices)
- Give FDA power of subpoena for documents and witnesses, as with other regulatory agencies
- Allow FDA to destroy imported drugs at the border valued less than \$2,000 that pose a health threat (so they don't get turned away, only to come back in through another port)

Create protections to allow FDA to exchange information with other regulators and receive information from whistleblowers

- Allow the FDA to exchange confidential information in a protected manner with other agencies and foreign governments, and to the public where warranted.
- Create protections for industry whistleblowers that wish to alert FDA to violations of the FFDCA and the Public Health Service Act.

Strengthen penalties to better deter crime and noncompliance

- Increase criminal penalties for knowing violations of the Federal Food, Drug, and Cosmetic Act to up to 10 years in prison and fines in accordance with title 18 of US Code. Knowing violations should include adulteration, misbranding, refusal of inspection, and counterfeiting
- Create civil penalties of \$500,000 per violation per day for drug-related violations of the FFDCA. Cap penalties at \$10,000,000 for a single proceeding that covers a number of violations
- Add asset forfeiture as a punitive measure for drug-related violations of the FFDCA

Increase FDA inspections of foreign manufacturing sites and improve oversight systems

- Require that all plants making finished drugs or active ingredients be inspected once every two years (or every four years if appropriate) – a standard more like that used inside the US
- Make delay or refusal of an inspection a prohibited act
- To facilitate tracking and oversight, require submission of unique ID numbers by manufacturing establishments, importers, and customs brokers.
- Create a dedicated foreign inspectorate within FDA

Create new industry registration fees to support FDA inspectional activities

- Fees will be set at the amount necessary to support increased drug safety activities and ensure that the added costs of manufacturing moving to low-cost countries does not create extra burden for taxpayers.

Mr. BURGESS. I now recognize myself for 5 minutes for questions. And again, Dr. Woodcock, welcome to our humble little hearing room here at the Energy and Commerce Committee. We welcome you back. Let me ask you a couple of questions that deal with the issue of conflicts and the exclusion of people from the FDA advisory panels because of conflicts of interest. Have there been instances where experts have been disqualified from serving on advisory committees because they served as an investigator for the product under consideration?

Ms. WOODCOCK. Yes.

Mr. BURGESS. Have there ever been instances where someone is disqualified because they have been in a clinical trial as an investigator for an unrelated product?

Ms. WOODCOCK. Yes.

Mr. BURGESS. So I think I have an accurate quote from you where you say it is difficult finding highly experienced people who do not have conflicts?

Ms. WOODCOCK. That is correct.

Mr. BURGESS. And we have delays in the panels because of this policy. And in fact your commissioner, Margaret Hamburg, Dr. Hamburg has said some meetings require expertise that is limited to a handful of experts who can often have conflicts of interest. So tell us what the real world consequences of this are. Most of us have never been in an FDA advisory panel meeting so what are the implications of having people that have to exclude themselves or be excluded because they either have knowledge of the product under consideration or they have been involved in an unrelated investigation?

Ms. WOODCOCK. We are asking the committee for advice on very complicated scientific questions. Our scientists are very well versed on the topic and will have gone over all the information in the application and any related literature. So they really want people at the table who can help them grapple with these complex questions and they would really like experts, trialists or disease experts who can shed additional light on the problem they are trying to deal with.

Mr. BURGESS. Just as someone from the outside, is the converse of that universe also true that the people who are involved may not have the knowledge set or skills to make some of the decisions they are required to make and in some cases maybe even lack the basic fund of knowledge to deal with the clinical question at hand?

Ms. WOODCOCK. Yes.

Mr. BURGESS. Thank you for that succinct and concise answer. Let me ask you this since you have given me the benefit of some time. I have been in a ping pong match for the past couple of weeks, couple of months, since the first of January when the EPA banned the sale of over-the-counter asthma inhalers. I am an asthma patient myself and I will just tell you all across this country people are going to be going to the CVS pharmacy at midnight because they have had an asthma attack and they are out of all of their other options and they are used to being able to buy for \$16 Primatene inhaler and now they cannot. And we as Members of Congress are going to start hearing about that. It is not going to happen all at once but it is slowly going to start rolling out into

the American landscape such that by the time of the August recess, I suspect there will be a number of people who show up in each Member's town halls complaining about this policy.

Now, we have heard from the EPA and the EPA says it is your fault, and Commissioner Hamburg said no, it is the EPA. Can you help us? Primatene has been on the market for a long time and the only thing that has changed is the propellant, CFC changed to HFA. I would argue that HFA is not as efficient a dispersant as CFC but that being aside, there really is no difference in the active pharmaceutical ingredient in the over-the-counter inhaler Primatene, but for whatever reason, it is held up somewhere. Can you help us get that done?

Ms. WOODCOCK. The switching of all the asthma inhalers was triggered by the Montreal Protocol that was agreed to by the United States to eliminate CFCs to help with the problem of the ozone layer. And FDA has gone through a very long process to inform the manufacturers, work with the community, prepare them, and then execute the switches. For the prescription albuterol inhalers, which are really a preferred standard of care, as you know, for asthma—

Mr. BURGESS. Yes, but I always don't plan ahead.

Ms. WOODCOCK. Right.

Mr. BURGESS. You know, I am the world's worst asthma patient and I will forget—

Ms. WOODCOCK. Right.

Mr. BURGESS [continuing]. And then something happens that triggers an attack at two o'clock in the morning and now the only option is to go to the emergency room and get a treatment and that is \$1,500.

Ms. WOODCOCK. I understand.

Mr. BURGESS. It was \$16, \$16.00 before, and this is what we have visited upon people. I do want to enlist your aid in getting this problem solved. I have asked the EPA to allow the sale of existing Primatene inhalers with CFC until those markets are exhausted, but we really do have to—that is why we have an approval rating of 8 percent because people look at this and say well, this is a simple problem. The stuff was for sale before, it has got a different propellant, sell it again. Or did you really think that asthma patients were blowing a hole in the ozone layer. I don't think so and you will never convince me otherwise. But my time has expired and I am going to yield to—who am I going to yield to? No one on your side. I will yield to Dr. Gingrey. Oh, I beg your pardon. OK, Dr. Gingrey, you are recognized for 5 minutes for questions, sir.

Ms. DEGETTE. I just want to welcome Dr. Woodcock.

Ms. WOODCOCK. Thank you.

Ms. DEGETTE. Thanks.

Mr. GINGREY. Mr. Chairman, thank you.

Dr. Woodcock, much has been made over the past months and years about drug and medical production moving overseas to countries like China and many reasons for this migration have been put forward. In a study that ran in Health Affairs—this is November 2011—entitled “Evolving Brand Name and Generic Drug Competition” may warrant a revision of the Hatch-Waxman Act. The au-

thors state that “the Hatch-Waxman Act in 1984 raises questions about whether the Act’s intended balance of incentives for cost savings and continued innovation has been achieved. Generic drug usage and challenges to brand name drugs’ patents have increased markedly, resulting in greatly increased cost savings but also potentially reduced incentives for innovators, new drug application, brand name. Congress should review whether Hatch-Waxman is achieving its intended purpose of balancing incentives of generics and innovation. It also should consider whether the law should be amended so that some of its provisions are brought more in line with recently enacted legislation governing approval of so-called biosimilars.”

Dr. Woodcock, do you believe that Congress should review the current Hatch-Waxman paradigm to ensure that the intended balance of incentives for cost savings and innovation continues to have been achieved?

Ms. WOODCOCK. I would say that deciding on those tradeoffs between innovation and cost saving for the American public is one of the jobs of Congress, and FDA will execute the provisions as they are laid out by the Congress. It is clear that there have been tremendous cost savings as many of the Members have indicated from the generics program. We also know that the innovator industry is struggling right now, and that again is multi-factorial and would have to be the subject of a different discussion. But the innovator industry overall is in a crisis.

Despite that, they have put forth many innovative drugs which we have been able to approve over the past year. We approved 30 new entities last year, many of them very innovative drugs. So whether that is the correct balance I think is a very complicated economic issue that I am not able to opine on, and it involves many societal tradeoffs to decide—

Mr. GINGREY. Well, I thank you and I know you can’t state exactly, but your answer certainly suggests that you have some concerns that maybe the balance that we are trying to achieve is not there. Is that a fair statement or—

Ms. WOODCOCK. I think many of us are concerned about the health of the innovator industry which is what brings new products and treatments and cures to people who lack therapies right now. However, whether or not Hatch-Waxman is the way to deal with that is beyond my purview.

Mr. GINGREY. Yes. Thank you, Dr. Woodcock. I want to commend the FDA on its concern for U.S. patients in light of our current drug shortage crisis. As you know, this is an issue that is important to this committee and this Congress and I want to commend my colleague, Representative DeGette, for her leadership in this area. As a medical provider, I believe that proper notification can play a critical role in ensuring patients get the best care possible, especially those with life-threatening conditions such as cancer. In your testimony, you state that “although many of the root causes of drug shortages are beyond our control, we are committed to addressing this important issue and look forward to working with the subcommittee on this issue. Tell me, Dr. Woodcock, what are the root causes of drug shortages and which ones are beyond our control?”

Ms. WOODCOCK. Well, I would refer you to the excellent document that was written at HHS, the Assistant Secretary for Planning and Evaluation, I believe, at HHS, that discussed this because many of them are economic issues. What we saw with the sterile injectables, which are the drugs that are in great shortage right now, was a surge in capacity over the past 10 years but with a very limited number of manufacturers, most of whom are in the United States. And with that capacity surge, they took on a large inventory of sterile injectables that they were producing, each of these manufacturers, and then when they developed problems in their manufacturing ability where they were getting particulates or endotoxin or other potential bacterial contamination, so forth, which I will add these things are hard to avoid and they take a lot of diligence to keep sterile manufacturing, you know, at a high quality level. But when they encountered these problems, then we lapsed into a shortage situation with a few alternatives or maybe no alternatives.

Mr. GINGREY. I see my time has expired and as I yield back, would you be sure and get that report to me? I would appreciate it.

Ms. WOODCOCK. Happy to do so.

Mr. GINGREY. Thank you. Mr. Chairman, I yield back.

Mr. BURGESS. I thank the gentleman for yielding. The Chair now recognizes Mr. Towns of New York for 5 minutes for the purpose of questioning the witness.

Mr. TOWNS. Thank you very much, Mr. Chairman. Thank you for having this hearing.

Dr. Woodcock, I am concerned about the large backlog of generic drug applications. What can be done about that?

Ms. WOODCOCK. Well, I am concerned about it, too, and the proposal that we have given to Congress for the Generic Drug User Fee Program has a specific provision to eliminate the backlog over the first course of that program.

Mr. TOWNS. Right. Is there cooperation across the board, you know, in terms of the pharmaceutical companies and all that? Everybody is on board with this agreement?

Ms. WOODCOCK. Yes, I think it is in everyone's best interest to eliminate this backlog and to have a predictable and efficient generic drug process.

Mr. TOWNS. Right. Once this goes into place, what will the turn-around time be approximately?

Ms. WOODCOCK. The goal time for any generic drug application is a first review, a complete response within 10 months of the submission of the application.

Mr. TOWNS. All right.

Ms. WOODCOCK. So the goal would be every generic drug applicant would get an answer back in 10 months and we would then look at how many of those could get right on the market or what were the problems that would keep them going into another cycle.

Mr. TOWNS. Right. Mr. Chairman, I am going to do something we don't do around here. I am going to yield back.

Mr. BURGESS. The Chair recognizes the gentleman's generosity and recognizes the gentleman from Ohio, Mr. Latta, for 5 minutes for questions.

Mr. LATTA. I thank the chairman.

And Dr. Woodcock, thanks very much for being with us today. I would like to kind of go back to what Dr. Gingrey was talking about at the very end in regards to drug shortages, and I have been working with several other members in the past few months on this issue. And first of all, you said in your opening statement that, especially on drug shortages, that we had a perfect storm. Could you describe what that perfect storm is or was?

Ms. WOODCOCK. Well, it was the enhanced utilization of the older sterile injectable drugs, OK, so the demand went up for them. At the same time, new sterile injectable drugs went generic, and so then firms took those on as well so then the demand on their lines—they have a limited number of manufacturing lines that can make sterile injectables, all right, because it is very hard to do that. So the demand went up, both for the existing drugs and the new generic drugs that were sterile injectables. At the same time, it takes a while to expand the capacity and bring up new facilities. So that did not happen.

And then manufacturing problems occurred within many of those lines, thus making them have to perhaps shut down the line and precipitate a sudden shortage. The other manufacturers who might take up the slack were also having capacity problems of their own and/or having manufacturing problems. So all these factors came together to create really an unprecedented amount of shortages that we are trying to deal with and shortages of drugs that Americans cannot do without.

Mr. LATTA. Let me ask, then, over the past year, what have you all done to alleviate that problem?

Ms. WOODCOCK. In 2011, 175 drug shortages were alleviated by our actions. Now, 86 of those I think were from one firm where we were able to do interventions, but we have multiple interventions as I describe but we can alleviate those. Nevertheless, there are several hundred shortages that are ongoing.

Mr. LATTA. Are there additional items that you can do then?

Ms. WOODCOCK. Pardon me?

Mr. LATTA. Are there additional items that you could work on to help on that issue?

Ms. WOODCOCK. Yes. Well, since the executive order by the President that asked firms to notify us of any kind of shortage and we have also put in a database that we are tracking these very carefully. We have added staff to the drug shortage program that we have at FDA. But we do feel that if there were legislation that requested companies or required companies to notify us, that would help us in perhaps averting more shortages.

Mr. LATTA. And also is there a disease area where there are more significant drug shortages than others?

Ms. WOODCOCK. Right now, we are hearing from the cancer community and that is because many of the cancer drugs are injectables. But the injectable drug shortage affects many other kinds of disease areas and over the years, historically, you couldn't predict where the shortages would arise. They have been in all sorts of disease areas.

Mr. LATTA. And also, will the generic drug user fee help with the drug shortage issue do you believe?

Ms. WOODCOCK. I believe that having a robust industry that has predictable timelines for its applications and can get applications through and also having an inspectional force that we can get out there quickly and do the inspections in the appropriate time will help with shortages because one of the things we need for shortages is we need more than one manufacturer that is able to make that drug. So if something happens at one plant, then there is somebody else who can ramp up production.

Mr. LATTA. OK. And some of the committee hearings and the press have suggested the key characteristic of the drugs in shortage older physician-administered drugs underscore failure in the older generic market and that incentives in this market are critical in solving the crisis. Do you agree with that assessment?

Ms. WOODCOCK. I am sorry. Could you repeat that?

Mr. LATTA. Yes. There has been in some of the committee hearings and also out in the press have suggested that the key characteristics of drugs in shortage older physician-administered drugs underscore a failure in the older generic market and that incentives in this market are critical to solving that crisis. And do you agree with that assessment?

Ms. WOODCOCK. I am not qualified to make a judgment on that being a physician and not an economist. The HHS report felt that it was a multiple number of factors and it wasn't simply an incentives problem. Theresa, do you have—

Ms. MULLIN. Yes, I think that that report would probably have the best description of all the kinds of factors. A number of them are economic and factors that are not within our ability to control and there may be other ways to address those but we have limited ability to address those factors.

Mr. LATTA. OK.

Ms. MULLIN. No ability in some cases.

Mr. LATTA. Thank you very much.

Mr. Chairman, I see my time has expired and I yield back.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentlelady from California, Mrs. Capps, for 5 minutes for questions.

Mrs. CAPPS. Thank you, Chairman, for recognizing me.

And Dr. Woodcock, thank you for your testimony today. I am actually going to just make a statement to add onto the list of reasons why the topic at hand, the drug shortages, is a very real issue. I would ask a question following but it has already been asked and you supplied the answer that I know you would answer to me. But it is such a prevalent problem plaguing manufacturers, hospitals, doctors, and patients alike. So this is a story of one of my constituents who reached out to our office. She is a pharmacy buyer at a nonprofit organization in my district which works with cancer patients. So right now, her organization is not able to purchase life-saving critical care drugs, and for some of them, they have been waiting more than 4 months. I know this isn't a new story to you either, but it is one more story. And the only route available for this organization because they are nonprofit is to get these drugs from the black market, who is essentially auctioning them off, often charging three times more than what they ought to cost. As a nonprofit, you can imagine they never are successful in their bids, and

instead, the treatments for their patients they are representing are delayed. This is hard to believe in this country at this moment.

So let me turn to something a little different—

Ms. WOODCOCK. May I say something?

Mrs. CAPPS. Of course, please.

Ms. WOODCOCK. We are accepting reports from outside parties where they have encountered excessive pricing behavior and other behaviors that we can refer to the Department of Justice.

Mrs. CAPPS. I appreciate that and actually will take that back to this constituent and to others who will let our district offices know when they hear these stories there is a path that can be followed. You don't just have to say I am so sorry. We can say, well, there is a path and there could be some recompense that is made in that area.

Another mechanism for helping to address drug shortages is notifying the FDA of impending shortages. I know that in the next panel, you are going to hear testimony discussing the Accelerated Recovery Initiative that the industry is putting forward to help address and prevent shortage, anticipating that might come up in their discussion. What do you think of this proposal, and in particular, do you think it should be implemented, in what ways would it obviate the need for legislation, and how is this going to help us so we can focus on things that would make a difference for you and that are going to come up with a solution?

Ms. WOODCOCK. Yes, we haven't had the opportunity to examine the proposal in detail and we look forward to working with the industry on the proposal as well as with Congress.

Mrs. CAPPS. OK. So you are going to be listening carefully to the next panel as well.

And then finally, with the rest of my time, we have heard a lot of discussion today about the increasingly globalized drug supply chain and the challenges it poses. I want to ask you about a couple of problems I have heard about in particular. First, I understand the FDA has had problems conducting or completing inspections of facilities overseas or abroad. Would you be willing to describe some of these problems such as if a foreign manufacturer doesn't allow you in to inspect its plant or unduly delays you for an inspection, what recourse do you now have and what additional authority would be helpful?

Ms. WOODCOCK. Mr. Beckerman will address that.

Mrs. CAPPS. Yes.

Mr. BECKERMAN. Sure. Currently, FDA has to show that a drug appears to be adulterated or misbranded to keep it out of the country, and if FDA inspectors are delayed, limited, or denied in the inspection, there is no immediate recourse that the Agency can take. And so having an explicit authority to allow us to exclude a drug if our inspectors have been impeded would be extremely helpful.

Mrs. CAPPS. So these companies know very well that if they delay or deny that nothing is going to happen anyway?

Mr. BECKERMAN. There are very different incentives depending on the type of inspections being done. Firms have an obvious incentive to let FDA investigators in for a preapproval inspection because that is a condition precedent to getting their drug on the

market. Once a drug is on the market, that incentive no longer exists and it would be helpful for FDA to have a tool.

Mrs. CAPPS. So having a tool would be useful to you to have?

Mr. BECKERMAN. That is right.

Mrs. CAPPS. I also understand that information sharing with foreign regulatory partners has posed some challenges. Could you describe a couple of these challenges—there are a few more seconds left—and also the role of importers in the supply chain that has become a more prominent one in recent years?

Mr. BECKERMAN. On the information sharing question, in particular the Food, Drug, and Cosmetic Act has a provision that prevents FDA from sharing what is called trade secret information, and this is not typically the sort of thing that we think about as, you know, the secret formula for Coke, but it is information related to the manufacturing process. It is critical to be able to share that information with regulatory partners if we want to take advantage of their regulatory reach and be as efficient as possible. So addressing the inability to share that sort of information would be very helpful.

Mrs. CAPPS. Would that require legislation?

Mr. BECKERMAN. It would.

Mrs. CAPPS. OK. Thank you very much. I yield back.

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

Mr. CASSIDY. Thank you, Dr. Woodcock. I am always impressed at how well you answer questions.

The gray market—I am speaking of course about drug shortages—what is the volume of drug on the—5—FU is in a shortage, do we have a sense of how much the gray market will arise to fill that need?

Ms. WOODCOCK. Well, I would ask Captain Valerie Jensen, who is our head of drug shortages. Do you have any insight into that?

Ms. JENSEN. Yes. I am Val Jensen, Associate Director of Drug Shortage Program, and we don't think there is a large supply in the gray market from what we understand about the gray market. FDA doesn't receive a lot of information about the gray market, but we do know that from what we hear, it is a very small volume that is in the gray market right now.

Mr. CASSIDY. Now, but I am concerned in this report of HHS, they speak about if there is early notification of shortages, there may be hoarding. That almost seems like you are throwing gasoline upon the potential of a gray market. Would you agree with that?

Ms. JENSEN. We would agree with that.

Mr. CASSIDY. And so it is good to have early notification or not?

Ms. JENSEN. So if we received the early notification, what we do with that is try to work with the company, whatever company is having the problem on addressing that issue as soon as possible. Hopefully, we can prevent the shortage before it even occurs. That is our goal.

Mr. CASSIDY. Now, I am also concerned, and I don't know this; I am just asking—do some people make it a practice to hoard in anticipation and therefore step in? It clearly would be a nice way to make some money. You mentioned there could be a referral to

DOJ, but this is kind of a late development. Have people done that in the past? Have we looked at the ordering patterns of companies? Do they order here, then they suddenly order there sort of thing?

Ms. JENSEN. FDA doesn't normally get that type of information, the ordering information.

Mr. CASSIDY. Would that be HRSA?

Ms. JENSEN. The manufacturers would know what is being ordered. When there is a potential shortage, sometimes companies do—

Mr. CASSIDY. But let me ask because I think here last time—and people have mentioned they don't know the source of drugs on the gray market—it seems logical to look at wait, who is ordering? Is there a difference in ordering pattern relative to a particular entity's patient base? Does that make sense? Now, that just occurs to me and frankly I have looked at that, and when you look at that, you think that is kind of interesting, small little hospital ordering a lot of drugs. Now, has anybody pursued that more than just kind of looking at it?

Ms. JENSEN. It is just not data that FDA has access to as far as hospital ordering patterns.

Mr. CASSIDY. I could give it to you. I mean I just made a phone call and got it and it actually just kind of raises questions frankly.

Ms. WOODCOCK. Right. Well, I think those are the types of things that law enforcement might be interested in. Also, I would say if we have early notification process, we would not plan to make it public unless we had failed to avert the shortage and the shortage was imminent.

Mr. CASSIDY. And again, as you were describing the means by which you averted shortage, there seems to be somewhat of an ad hoc basis to it. You got a call, you rushed in, you started making it. In my life I have learned that it is better to have a system as opposed to an ad hoc. Now, do you systemize that or is it still somewhat ad hoc?

Ms. WOODCOCK. I think we have systematized it to the extent it is possible. The problem is that the manufacturers cannot predict when they are going to run into shortage. Many of these shortages are precipitated by manufacturing failures. They make the drug, they are going along making the drug, everything is fine, and then they discover particulates, they have mixed up the drug—

Mr. CASSIDY. Presumably there is quality control that on a regular basis they are going to pull up and say, OK, every 6 weeks we are going to, you know, run a sample and make sure it doesn't have sporadic or something in it.

Ms. WOODCOCK. Well, it is much more than that actually. There is a very tight system of controls. You were talking about the good manufacturing processes call for very tight controls—

Mr. CASSIDY. I only have 53 seconds. By the way, just to go back, if you don't have access to the ordering pattern of the hospitals, who does have that data?

Ms. JENSEN. Yes, I think we would have to look into that.

Mr. CASSIDY. Could you let me know that? I would be really interested in that.

Let me ask one more thing. Going back, Mr. Dingell had a line of questions about whether or not you need more resources. I think

it was our previous conversation you mentioned that union contracts would limit the ability to send people overseas. Dr. Hamburg was here and she really kind of rope-a-doped me on that, so let me just ask a yes or no. Do you have the ability under your union contract to send somebody overseas to inspect a plant if they otherwise object? Yes or no?

Ms. WOODCOCK. I don't know the answer to that. I don't supervise the field staff. And I imagine it depends on the circumstances. So I can get back to you but I can't answer that straight out.

Mr. CASSIDY. Does anybody on the panel know that? OK, if you could, I would appreciate that.

Ms. WOODCOCK. Certainly.

Mr. CASSIDY. Thank you. I yield back.

Mr. PITTS. The Chair thanks the gentleman. That concludes the members of the subcommittee questioning.

Without objection, we will go to the members of the full committee. Ms. DeGette of Colorado is recognized for 5 minutes for questions.

Ms. DEGETTE. Thank you, Mr. Chairman.

I just want to ask a follow-up question about the drug shortages and I appreciate my colleagues on both sides of the aisle working with me on this issue because it is something that sort of hit and escalated, and we are all hearing about it from our hospitals. And, you know, we are all concerned about the stories we hear, particularly with these generic injectables, about the shortages that hospitals are having. A lot of them are pediatric cancer patients and other patients like that. But I am hearing from my pharmacist at the hospital that this is now expanding to many other drugs. They told me that they have a drug shortage a day at some of these hospitals, some place where they are trying to make these value judgments about what they treat the patients with. And so I also am concerned about the hoarding issues and the other issues, but I guess I would ask you, any of the witnesses, to talk about under the current voluntary program that you have, do you see a lot of problem with hoarding right now?

Ms. JENSEN. We do receive reports from pharmacists, mostly faxes and emails that they have received from gray marketers, from companies advertising these drugs at very high prices, and we do forward all of those reports to the Department of Justice.

Ms. DEGETTE. And have you seen a large incidence of that?

Ms. JENSEN. We have—

Ms. DEGETTE. OK.

Ms. JENSEN [continuing]. Over the past—

Ms. DEGETTE. And do you think there are some ways we can write legislation so we don't experience a lot of hoarding if we make a mandatory reporting program?

Ms. JENSEN. So with notifications of mandatory reporting, we would not post a shortage until we know that shortage is going to occur, absolutely going to occur, or has already occurred. We would want to hold off because our goal is to try to prevent all shortages. If we can do that through working with the manufacturers, through working with alternate manufacturers to ramp up, as well as sometimes having to temporarily import product, that is what we are doing.

Ms. DEGETTE. So your process would be if you got notification of a shortage to contact the manufacturers to see if it could be resolved internally—

Ms. JENSEN. Absolutely.

Ms. DEGETTE. It is a little bit of a waiting game, isn't it, because if you don't notify the hospitals and the physicians quickly enough, then having any kind of a notification system is pointless, right?

Ms. JENSEN. Right.

Ms. DEGETTE. So you are going to have to figure out how to do that.

Ms. JENSEN. We need a good way to get information out when we know there is going to be a shortage, get it out as quickly as possible so that hospitals can make decisions.

Ms. DEGETTE. And what would happen if you did have a system where you could get that notification out? What would the hospitals then do with that information?

Ms. JENSEN. Well, they could plan accordingly. Sometimes treatments can be reserved for certain types of patients where there is an alternative for other patients. They can use those alternatives. Sometimes it helps hospitals make those decisions.

Ms. DEGETTE. OK. Dr. Woodcock, in your written testimony, you had said that the FDA sent a letter to the pharmaceutical manufacturers reminding them of their current legal obligations to report certain discontinuances to the Agency and urging them to voluntarily notify the FDA of all potential disruptions of the prescription drug supply to the U.S. market even when disclosure is not currently required by law. After you did that, you said that there has been a significant increase in the number of potential shortages reported to the FDA. So my question is, is it your sense that manufacturers were not complying with current law before they got that letter?

Ms. WOODCOCK. Our sense is I think that manufacturers were complying with current law, but the current law only has a limited universe of things that have to be reported. And we asked for voluntary reporting of a much wider universe.

Ms. DEGETTE. So as I understand it, the Agency cannot expand the reporting, cannot require more reporting without authorization from Congress, is that right?

Ms. WOODCOCK. Not more mandatory reporting.

Ms. DEGETTE. Without authorization from Congress, right? OK. Thank you very much.

Thank you, Mr. Chairman. I yield back.

Mr. PITTS. The Chair thanks the gentlelady. The Chair recognizes the gentleman from Illinois, Mr. Shimkus, for 5 minutes for questions.

Mr. SHIMKUS. Yes, I am sorry, Dr. Woodcock. I know you have been here for a while. I had to go speak on Yucca Mountain, so I had my different jobs I have to do.

So I just really wanted to focus on Generic User Fee Act issues and the proposal to develop better science for new bioequivalent methods for locally acting drugs. So how do we know what the promises are? So what types of metrics do you think there will be for Congress and the American people to judge whether we are getting our best return on investment with this?

Ms. WOODCOCK. Well, similar with the user fee program, you know, there are interim goals throughout this Generic Drug User Fee Program that have been devised, and we will report on those goals and you will know exactly what our performance is against the goals. So there are many metrics that are put into place for performance of the program. We intend to meet those metrics, but right from the beginning, we will have to do things in the first year, and we can report on those actions.

Mr. SHIMKUS. Yes, and I appreciate that. I think Congress would like to see I think the folks who are working with you collaboratively would like to make sure that is transparent, there is predictability. A lot of our concern is the length of time without it. So I mean there is just hope that in paying for an expedited, clear, safe system, that we are going to get what is going to be paid for.

Ms. WOODCOCK. Well, I hope you can feel some confidence because of our track record of the Prescription Drug User Fee Program where we have exceeded or met our goals up through almost the entire program.

Mr. SHIMKUS. And I mentioned this numerous times in various hearings and I applaud it; I think focusing on the risk-based approach in the recent reports is right on. I mean if good actors are good actors and they have been good actors, they continue to be good actors, then there may be a time to revisit but annually may—we can make that determination. Obviously, when we are not inspecting, we would much rather have inspections of facilities we haven't even visited versus continually re-inspecting the good actors. So I find that a positive and I look forward to that.

Utilizing prediction information from companies, foreign governments, and third parties could help us, obviously, to do this risk-based system. Can you describe the importance of the risk-based approach in ensuring the safety of imported drugs?

Ms. WOODCOCK. Certainly. What we know about facilities is that if they are having problems, they may not correct them and the problems may get worse. So we go into a plant initially, we discover problems, if we don't go and return and verify that they are on an improvement trajectory, we may be seeing a situation where the production methods may be deteriorating. And so it is very important for us to go sort of where the money is, where the risk is and to be able to follow up on those facilities that are subpar, all right, and also to follow up more closely on those facilities that are producing riskier products such as the sterile injectables to make sure they are continuing to meet their obligations.

Mr. SHIMKUS. And I appreciate that. And my last question is how can we leverage the third party actors or foreign governments? Help me talk through how do we get a little more buy-in or can get them to understand the importance of what we are trying to do.

Ms. WOODCOCK. The foreign governments?

Mr. SHIMKUS. Right, or other third party entities that may be involved.

Ms. WOODCOCK. Other third parties, um-hum. As Mr. Beckerman said, we would like to have better ability to exchange information with foreign countries who have inspectorates. Many countries now are developing pharmaceutical inspectorates. They go to the fac-

tories; they have information. We do get heads up from them when there are problems, but we would like to have a much better global safety net so that all the regulators are working together and any other inspectorates that might be out there, third party inspectorates. So we share information and we make sure around the world that that safety net exists.

Mr. SHIMKUS. Yes, historically, I think we have all believed that FDA has been really the gold standard. I think the EU is because of their timeliness is getting into a competitive arena with us. We would like to continue the gold standard and maybe push those values but also a timely process so we don't lose that leverage.

Thank you, Mr. Chairman, and I yield back.

Thank you, Dr. Woodcock.

Mr. PITTS. The Chair thanks the gentleman. And that concludes panel one. Do we have another one? I am sorry. I didn't see you.

The Chair recognizes the gentleman from New York for 5 minutes for questions.

Mr. ENGEL. Thank you, Mr. Chairman. It is hard to see on the side, I know. Thank you.

Dr. Woodcock, several of the witnesses in the second panel in their written testimony mention that the user fees included in GDUFA and BsUFA are meant to be in addition to a solid base of annually appropriated funds for the FDA. So I was pleased to see that for the fiscal year 2012 the FDA received a 50 million increase in funding over fiscal year 2011 funding levels. But this was a hard-fought victory given that the first proposal was a 285 million cut in FDA funding. So could you elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact the Center for Drug Evaluation and researchers' ability to meet the review time frames and inspection standards outlined in the GDUFA and BsUFA user fee agreements?

Ms. WOODCOCK. Yes. All of the user fee programs assume that there is an appropriated base funding that we build on and that is augmented by the user fees. As I think the discussion on drug shortage has illustrated, FDA has many other jobs, and the drug program has many other jobs other than simply review. And for the health and safety of our population, we need to do all those activities well and we do need resources to do them. So the Generic Drug User Fee Program that is being proposed is built upon a platform of appropriated dollars and is additive. The Prescription Drug User Fee Program has always had a trigger and is of appropriated funds and the fees are additive that allow us to meet the goals and accomplish all that ambitious program. And similarly, for biosimilars it will be built on an appropriated base.

Mr. ENGEL. Well, thank you. You mentioned the drug shortages. The largest employer in my district is Montefiore Medical Center in Bronx, New York. They are, as you know, a premier academic medical center with centers of excellence in cancer care, cardiovascular services, pediatrics, transplantation, and neurosciences, and my constituents have really come to rely on them. All three of my children were born there and they are really, really a treasure. When I asked them about the impact of drug shortages on Montefiore, they estimated to me that members of their staff, including pharmacists and physicians, spent more than 110 hours a

week addressing issues directly related to drug shortages. So clearly this issue, dealing with this, requires a significant amount of people power and labor costs in order to track down medications. Can you describe the steps the FDA is taking to assist our hospitals like Montefiore in staying on top of current and anticipated drug shortages?

Ms. WOODCOCK. Certainly. We sent a letter out to all manufacturers reminding them of their statutory obligations and asking them to voluntarily notify us in advance of potential shortages so that we can do what we do to mitigate them. We work with manufacturers to mitigate. We have even allowed drugs to be shipped with filters, with instructions to filter the drug because it had particulates if we were sure that the filter wouldn't take out the agent as well and we had verified that. So we do those risk mitigation efforts. We even allow importation of unapproved drugs from other countries temporarily to fill the gap for our patients. And we have a web page and we work with the associations and with the physician community to try and figure out how to mitigate these shortages. But at the end of the day, if there is no drug there that can be had, we are all in trouble.

Mr. ENGEL. I agree. Let me ask you this final question which also ties in with the drug shortage problem. I have heard from healthcare providers and patients that there is an added layer of difficulty in addressing shortages in this area because they say that the DEA limits the amount of active pharmaceutical ingredient a company can purchase and manufacture. I have also heard from parents who are frustrated when they have struggled to obtain generic forms of their children's ADHD medications in recent months. So I do recognize that the DEA has to do its part to ensure that controlled substances are not being abused, but how can DEA and FDA work together to ensure that the shortages of controlled substances such as the ADHD medications or pain medications like fentanyl are quickly addressed and access to these to patients with a clear need?

Ms. WOODCOCK. Yes, we worked very closely with the DEA, and my understanding is that the manufacturers have received their 2012 quotas for the ADHD drugs and we expect that situation to be ameliorated very rapidly. But we do work very closely with them. We provide information to them every year that is very relevant to them setting the quotas of these various drugs, how much we expect will be needed. So we have a very close relationship.

Mr. ENGEL. OK, thank you.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

OK, I think that concludes panel one. The Chair would like to thank Dr. Woodcock and her panel for your excellent testimony.

Ms. WOODCOCK. Thank you.

Mr. PITTS. And excuse panel one and call panel two to the witness table. And while they are coming, without objection, the chair would like to enter into the record four documents: a statement by the American Academy of Pediatrics, one by the American Society of Health System Pharmacists, another by the National Community Pharmacists Association, and one by the Biotechnology Indus-

try Organization. And it has been shared with minority. Without objection, they will be entered into the record.
[The information follows:]

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

Testimony for the record

On behalf of the
American Academy of Pediatrics

Before the
**Energy and Commerce Committee
Health Subcommittee**

February 9, 2012

Mr. Chairman, members of the subcommittee, the American Academy of Pediatrics (AAP), a non-profit professional organization of 62,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists, thanks you for the opportunity to submit testimony for the record on the issue of drug shortages.

Pediatricians throughout the country are experiencing firsthand the impact of drug shortages on the practice of pediatrics. Shortages, discontinuances, or interruptions in the pediatric drug supply have and will continue to put our patients at risk. Past and current shortages have forced pediatricians to rely on alternative therapies, if they exist. In many cases, these alternatives may be less than ideal for our patient populations and their safety and efficacy in pediatrics may not be known.

The AAP has worked for decades to ensure that medicines used in children are studied in children. The physiology of children is different than that of adults and this changes how they absorb, metabolize, eliminate, and respond to medications. It is because of these significant differences that it is important to remember that children are not just little adults, and that they must, wherever possible, have the benefit of age-specific therapeutic safety and efficacy data.

We thank the subcommittee and the leadership of Representative Anna Eshoo for their support for two laws, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), that have taken giant strides towards achieving this goal. Since BPCA was enacted in 1997, 426 drug labels have been updated with pediatric information under BPCA and PREA. With this new pediatric information, off-label use of drugs has gone down. However, because half of drugs used in children still lack pediatric labeling, off-label use remains an unfortunate but necessary practice. The AAP looks forward to working with the subcommittee to renew and strengthen these laws before they expire on October 1 of this year.

Impact on Pediatrics

In recent years, many of the drug shortages have directly impacted children. More than two years ago, there was a widespread national shortage of 0.5% erythromycin ophthalmic ointment due to manufacturing changes. Four million children each year need erythromycin ophthalmic ointment for prophylaxis of ophthalmia neonatorum due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. If left untreated, it can cause blindness. Some states mandate this treatment.

At the time of the shortage, the two other products with efficacy against *N. gonorrhoeae* were no longer available in the U.S. The government did not appear to have anticipated the shortage and it took pressure from the AAP and others for federal agencies to develop and

release recommendations for an alternative prophylaxis regimen. However, at that time, there were no safety and efficacy data for the alternative products.

The AAP is closely monitoring the ongoing shortage of parenteral vitamin K. Recently, many hospitals have begun to face a declining supply of parenteral vitamin K which is routinely administered to nearly all newborns. The injectable form is the recommended method of administration to newborns. Due to the developing shortage, some hospitals have begun to conserve their supply by giving the vitamin K injections only to those infants in the neonatal intensive care units and using an oral preparation for healthy newborns. We are aware of at least one example where providers were forced to dilute an adult preparation. With dilution, errors can and do occur.

Additionally, pediatricians, especially neonatologists, have experienced shortages of component ingredients for a life-saving treatment for neonates, total parenteral nutrition (TPN), which is used in babies who cannot yet eat and have no alternative nutrition source. Last spring, the manufacturer of component ingredients of TPN announced a nationwide voluntary recall. In some cases, they were the only manufacturer in the U.S. marketplace resulting in prolonged periods of no new supply. Among the ingredients in short supply are sodium chloride, calcium gluconate, phosphate (sodium and potassium), selenium, magnesium sulfate injections, and others. To date, supply is still not what it was prior to the voluntary recall. For newborns that rely on TPN intravenously as their source of nutrition, availability of these component ingredients is truly a matter of life or death.

Drug shortages impact general pediatricians and subspecialists alike. At present, pediatric rheumatologists are reporting shortages nationally of injectable methotrexate. Pediatric oncologists have been facing shortages of cytarabine, daunorubicin and other critical products where there are limited or no alternatives. Pediatric anesthesiologists are reporting significant shortages of fentanyl and sufentanil which has the potential to have a huge impact on the ability to provide safe and effective anesthesia and postoperative sedation for pediatric cardiac patients and sedation for intensive care unit patients. The lack of viable alternatives can pose a huge risk to these patients.

The Academy is also receiving regular reports from its members on nationwide shortages of medications to treat children with attention deficit hyperactivity disorder. Unlike other shortages, this one is made additionally complex by the overlapping authorities of FDA and the Drug Enforcement Agency. The AAP is interested in trying to find relief to this shortage and all others that are currently ongoing.

But whether it is the propofol shortages that have had a profound impact on pediatric anesthesiology or persistent shortages of antibiotics such as intravenous preparations of trimethoprim/sulfamethoxazole or amikacin, drug shortages are increasingly more

common. Among pediatric products that are in short supply, the intravenous preparations appear to be disproportionately over-represented.

The AAP welcomes the opportunity to explore with the FDA and others the causes behind these shortages as well as solutions for preventing and addressing them.

Prevention

The AAP believes that a comprehensive solution to drug shortages must include provisions that prevent the shortage from occurring in the first place. Notification of physicians and pharmacists of drug shortages after the fact, as is all too often the case, frequently compromises care and puts patients at risk. We urge FDA to develop and maintain a list of critical medications that should specifically include medications used in pediatric populations. For pediatrics, such a list should not be limited to the labeled indication of the product since so many products used in children, especially neonates, are not labeled for their use. Among the products that should be included in the critical drugs list are those which come from a sole manufacturer.

Once this critical medications list is developed, FDA, working with other federal partners, should determine how much of the product is necessary to have on hand to meet demand in advance of a potential shortage, discontinuance or interruption. This list should be informed by the current rate of use of these drugs and by the time required to replenish the supply, allowing extra time for both. Then FDA and its partners should establish a mechanism for the purchase and storage of advance supplies of the critical medications on this list. AAP recommends FDA and its federal partners consider the creation of a National Critical Medication Stockpile, using the Strategic National Stockpile as a model.

FDA should develop and maintain a database containing information about the domestic and foreign manufacturers for all of the items on the critical medications list, regardless of whether their products are approved in the U.S. Over time, FDA should take steps to work with manufacturers so they can meet U.S. standards for safety and efficacy. Other efforts to increase supply should be explored especially since unanticipated natural or man-made disasters can and do happen in the U.S. and around the world, and these disasters can have a significant impact on the supply of component ingredients or finished products.

Distribution

The AAP is concerned about inconsistent distribution or maldistribution of products that are in short supply. We urge the FDA and its federal partners to establish a process to ensure fair and equitable distribution of products that are experiencing a shortage, discontinuance, or interruption. We also hope there will be strong national safeguards in

place to protect against hoarding or price gouging. For products on FDA's critical medications list, it may be helpful for FDA or one of its federal partners to maintain a real-time map allowing purchasers to know where products can be found and in what quantity.

Communication

The AAP is deeply concerned about FDA's current system for alerting pediatricians to potential or actual shortages, discontinuances, or interruptions in supply of pediatric products. The current system is simply too passive. We urge the development of a system for real-time, bi-directional exchange of information between federal agencies and providers because in some cases health care providers are the first to learn about a change in supply. The critical medications list should be used to then develop a network of health care providers for each class of products that would be contacted immediately about a potential supply shortage, discontinuance, or interruption. Communication about shortages to the FDA by manufacturers and from the FDA to providers should not be limited to on-labeled indications since half of all drug used in pediatric patients are used off-label. In neonatology, almost 90% of the agents that are routinely administered to neonates (babies from birth to 1 month) have never been adequately studied and labeled for safety, dosing, and efficacy.

Addressing the Shortage

Once the shortage, discontinuance, or interruption in supply has occurred, we urge the FDA to work more quickly with companies to restore their ability to manufacture safe and effective products. Special attention and urgency should be paid to the products on FDA's critical medications list. Because the lack of supply for certain critical products can represent a threat to the public health, we recommend FDA explore the use of authorities such as Emergency Use Authorization or personal importation provisions to allow for additional supply to enter the U.S. market from other manufacturers under time- and quantity-limited circumstances.

There have been instances where no new supply is available and no alternative manufacturer exists in the U.S. Therefore, FDA and its federal partners should work much faster to identify recommended alternative therapies and communicate them broadly to the public, especially the provider community. Wherever possible, the FDA and its federal partners should utilize outside subject matter experts when developing these recommendations or guidance for alternative therapies. For products on FDA's critical medications list, alternatives should be identified by the federal government prior to onset of a shortage, discontinuance, or interruption.

The AAP looks forward to working with the subcommittee on this important issue that has greatly impacted the care we give our patients.

House Energy and Commerce Subcommittee on
Health

Hearing to

Review of the Proposed Generic Drug and
Biosimilars User Fees and Further Examination of
Drug Shortages

February 9, 2012

Statement for the Record
Submitted by the



American Society of
Health-System Pharmacists®

American Society of Health-System Pharmacists

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The American Society of Health-System Pharmacists (ASHP) respectfully submits the following statement for the record to the House Energy and Commerce Committee's Subcommittee on Health hearing to review proposed generic drug and biosimilar user fees and further examination of drug shortages.

As the national professional association representing over 35,000 pharmacists who practice in hospitals and health systems, ASHP can offer unique and vital feedback on this important health care issue. Pharmacists in hospitals and health systems are experts in medication use who serve on interdisciplinary patient-care teams. They work with physicians, nurses, and other health care professionals to ensure that medicines are used safely, effectively, and in a cost-conscious manner.

The scope and severity of drug shortages is well known and its impact has been felt by patients, caregivers and others throughout the supply chain. ASHP has commented extensively on the causes of drug shortages, their impact on patient care, and potential policy options to address the problem to both Houses of Congress and the FDA. Therefore, we are not including the background information stated in prior written and oral testimony but would refer you to our web site as a reference for additional background information if you need it:

<http://www.ashp.org/DocLibrary/Advocacy/SenateFinanceComm-on-Drug-Shortages.aspx>.

Instead, we are providing direct examples of policy options we believe Congress can enact now to begin to alleviate drug shortages. Furthermore, given the scope and complexity of the ongoing Prescription Drug User Fee Act (PDUFA) negotiations, we strongly urge Congress to act now on the issue of drug shortages, even if it means moving legislation independently of PDUFA, as patient safety and public health concerns continue to worsen.

The causes of drug shortages are multifactorial, and solutions will likely involve not only Congressional action, but also action by FDA and the market itself. However, there are policies that we believe Congress can and should pursue to help address this ongoing crisis.

First, we urge Congress to enact the early warning system as described in H.R. 2245, the Preserving Access to Life-Saving Medications Act. It has been well documented by FDA that when the agency has information about production interruptions and product discontinuations in advance, it can work to prevent shortages. Further, we believe the provision requiring manufacturers to work with FDA on developing contingency plans to ensure supply of medications is a critical piece that may help to prevent shortages from occurring in the future.

Second, Congress should examine the current quota system in place by the Drug Enforcement Administration (DEA) as a potential factor in shortages of controlled drugs.

While we have no specific data to suggest that DEA quotas are causing shortages, other members of the supply chain have identified this as a potential barrier. We commend Congresswoman DeGette and Congressmen Waxman, Pallone and Van Hollen for their recent letter to DEA asking the agency to provide more detail on how it determines quotas, how often quotas are adjusted and the associated regulatory burden for industry, and potential impacts quotas have on patient care.

Likewise, we commend those same members for their letter to Shire Pharmaceuticals asking the company to shed light on how it allocates the production quotas set forth by DEA in the manufacturing of its various ADHD products. Given that there appears to be two conflicting points of view on the impact the quota system has on drug shortages, ASHP is greatly interested in the responses of both DEA and Shire Pharmaceuticals to those specific questions.

Third, a newly-introduced bi-partisan bill (H.R. 3839) by Congressmen Carney and Buschon, would direct FDA to establish a national critical drug list and a national critical drug shortage list. The national critical drug shortage list would be communicated to the public with information on the severity and duration of the shortage, reason for the shortage, identification of alternate therapies and specific regions of the country impacted by shortages. ASHP is generally supportive of this approach; however, FDA does not provide information on any unlabeled medication indication or unapproved medications, as some medically necessary drugs are unapproved, and unlabeled or unapproved use of medically necessary drugs is common (for example pediatrics), therefore, FDA cannot provide this information. In addition, FDA may be constrained in providing recommendations for alternative therapies due to potential conflict of interest. The University of Utah Drug Information Service does provide the public with information on alternate therapies for drugs in short supply. Given this fact, ASHP and the University of Utah maintain close communication with FDA on our efforts to track shortages. We believe that this would likely continue if this provision was enacted due to our clinical expertise, and FDA's ability to obtain information about duration and severity of shortages.

ASHP also supports the provisions in the bill which creates a feasibility study on stockpiling and directs the Attorney General to increase controlled substance quotas if warranted. While we believe a national stockpile for anticipated drug shortages is difficult to achieve, it may be worth further investigation as a study may shed light on alternatives to a stockpile that were not previously conceived.

Fourth, the inclusion of a generic user fee program in the upcoming PDUFA reauthorization may allow FDA to leverage these user fees as economic incentives for manufacturers. For example, the agency could offer reduced application fees for products in short supply, or discounted fees if a company demonstrates that its contingency plans are sufficient to reduce the risk of a shortage if production is halted. While this policy option does rest within the PDUFA reauthorization process, we believe a generic user fee program can provide a crucial economic tool for FDA to provide incentives to manufacturers.

Conclusion

ASHP remains pleased by the high level of attention Congress and the subcommittee has given to the drug shortage crisis. The hard work of your staff and the input provided by those most affected by these shortages has given us a blueprint to move forward, and we urge Congress to do so as quickly as possible. We fully recognize that the options outlined above are not a complete solution. However, they represent initial policy options that can be enacted immediately while we further examine additional solutions.



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**United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health
Hearing on "Review of the Proposed Generic Drug and Biosimilars User Fees
and Further Examination of Drug Shortages"
February 9, 2012**

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

Effect of Drug Shortages on Community Pharmacy and Patients

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

As community pharmacists are on the frontlines of health care delivery, our primary goal is to provide timely and continued access for patients to the life-saving medications they need. To date, most prescription drug shortages have had a greater impact on hospital and health system pharmacies, with almost all hospitals reporting at least one drug shortage in the previous six months.¹ However, these shortages are not confined to in-patient needs.

A NCPA survey of community pharmacies, conducted in January 2012 (results attached), revealed that 96% of nearly 700 respondents experienced a drug shortage in the past six months. Moreover, 59% of respondents stated that over the past six months, they have been experiencing drug shortages daily, whereas 23% have been experiencing drug shortages weekly. Products used to treat attention deficit hyperactivity disorder (ADHD) account for the largest class of drugs NCPA members have experienced shortages with, with 82% of respondents stating they experienced a shortage of ADHD medications, 88% of which were generic ADHD medications.²

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

² NCPA Drug Shortages Survey, January 2012

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Both out-patient and ambulatory patients suffer when oral chemotherapy, specialty drugs, and products to treat ADHD, among others, are scarce on the market. In fact, 66% of respondents to the NCPA survey stated that patients go without their prescription being filled at their pharmacy as a result of the shortage. Even if there are alternative therapies available, insurance companies will not always pay for these alternative therapies. According to the NCPA survey, 52% of respondents stated that insurance companies do not cover an alternative therapy and that the patient is burdened with the responsibility of paying cash for such alternative therapies.

How Community Pharmacies Respond to Shortages

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

In addition, community pharmacists may be able to provide compounded products, depending on the nature of the shortage. In some cases, the raw materials to manufacture a scarce product are not available meaning that compounding pharmacies will not be able to supply the needed drug. Compounding pharmacies may be able to provide compounded prescriptions for patients when raw materials are available and they comply with the laws differentiating compounding from manufacturing.

Independent community pharmacies can provide valuable services to their patients in times of certain shortages. Results of the NCPA survey reveal that 63% of respondents contact a secondary or backup distributor in times of shortages, 58% call a competitor, and 13% compound the medication.

Significant Cost Increases to Patients, Payers, and Pharmacies

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

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

Community pharmacists have always helped their patients decide if a generic drug is safe and appropriate and have higher generic dispensing rates compared with pharmacy benefit manager (PBM) mail order facilities.

Recent data confirms that the generic dispensing rate of community pharmacies is at least 10 percentage points higher than the mail order generic dispensing rates of the three largest PBMs. However, as generic prices have increased in some cases due to shortages, PBM payments to community pharmacies have not kept pace.

Price fluctuations resulting from generic drug shortages prompt higher acquisition costs for these sparsely available products. According to the NCPA survey, 81% of respondents stated that they had observed price fluctuations associated with drug shortages, which resulted in higher drug acquisition costs. If PBMs don't update their prices at the same time, generic dispensing is threatened. Unfortunately, this is exactly what is occurring, as 62% of NCPA survey respondents stated that PBM reimbursements were not reflecting the acquisition cost increases that resulted from drug shortages. These unforeseen consequences of drug shortages can therefore have a huge impact on all involved in the drug distribution channel, especially on community pharmacies and our patients.

Legislative Proposals to Preserve Generic Dispensing Rates in the Face of Shortage-Induced Price Increases

To address the problem in which drug shortages lead to higher pharmacy acquisition costs, while reimbursements lag, NCPA has developed two legislative proposals that would remove the threat of lower generic dispensing rates in times of drug shortages. First, in the context of the Medicaid program, we propose to suspend the federal upper reimbursement limit ("FUL") for critical access drugs, i.e. drugs facing shortage problems.

Presently, the relevant statutory provision requires States to set their maximum allowable cost ("MAC") reimbursement based on the FUL amount. The FUL standard, in turn, is calculated based on the average manufacturer price ("AMP"), which is a lagging standard that is several months old. Since the FUL and MAC reimbursement standards are based on the lagging AMP standard, the FULs and MAC reimbursements lag in terms of how much they reflect real-time prices.

This pricing/reimbursement dynamic causes major problems within the context of a drug shortage involving critical access drugs. When a drug becomes a critical access drug the acquisition cost may immediately skyrocket, but the FULs and MACs will not adjust for those changes until months later. Therefore, pharmacies end up purchasing critical access drugs at suddenly high prices, while the reimbursement remains the same and fails to adjust. Accordingly, our proposed statutory amendment would suspend limiting reimbursement in Medicaid to the FUL for any critical access drug and would require the Secretary to establish a new benchmark for reimbursement for those drugs, which reflects the changing costs of those drugs.

Our second proposal would address this same shortage induced pricing/reimbursement dynamic within the context of the Medicare Part D program. This is accomplished by requiring more frequent updates by Part D plans to their MAC reimbursement standards, along with government oversight over this process.

Presently, contrary to law, Part D plans do not provide weekly updates to their MAC reimbursement standards, nor do they provide transparency regarding the methodology for how their MACs are set. Similar to the Medicaid context, when acquisition prices for a Part D drug go up, it is generally observed that the Part D MAC reimbursement rate for that drug lags for weeks or months before it reflects the drug price increase. The lag in MAC reimbursement updates is particularly problematic in the case of critical access drugs subject to drug shortages because those drugs are subject to sudden significant price increases. In such situations, the MAC reimbursement may not be enough to even cover the actual cost of the drug. Our proposal seeks to resolve this problem by requiring Part D plans to submit to CMS their MACs for critical access drugs on a regular basis, and by requiring CMS to ensure that the MAC reimbursements reflect the actual current market prices of the critical access drugs.

Conclusion

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



NCPA Drug Shortages Survey Results January 2012

Drug shortages are not just impacting hospitals and health system pharmacies; community pharmacies are increasingly facing drug shortage problems as well.

NCPA surveyed our members in January 2012 regarding drug shortages and received a total of 675 responses. These survey results provide important information about drug shortages in the independent community pharmacy setting, which dispenses nearly 40% of all retail prescriptions. Drug shortages have resulted in pharmacies' scrambling to obtain a dwindling supply, an inability to fill prescriptions, higher acquisition costs, a lack of patient insurance coverage for alternative drugs, and more, all of which may result in the patient going without their necessary medications. Ultimately, drug shortages negatively affect patients and the pharmacists' ability to provide patient care.

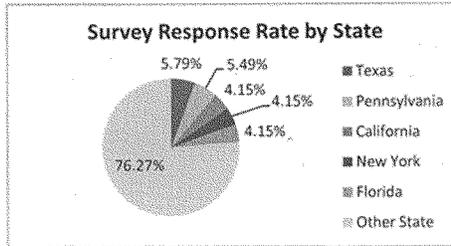
The survey contained specific questions related to shortages of drugs used to treat attention-deficit hyperactivity disorder (ADHD), as this class of medications has been associated with increased scrutiny related to shortages.

Key Highlights

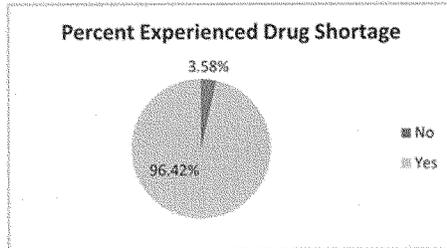
- 96% of respondents have experienced a drug shortage in the past six months.
- 82% of respondents stated that they experienced a shortage of ADHD medications in the past six months – 88% of which were generic drugs – followed by topical creams/ointments (31%) and specialty medications (13%).
- 59% of respondents stated that over the past six months, they have been experiencing drug shortages daily, whereas 23% have been experiencing drug shortages weekly.
- 58% of respondents stated the average length of a drug shortage is more than a month, whereas 22% stated drug shortages last an average of three to four weeks.
- 66% of respondents stated that patients go without their prescription being filled at their pharmacy as a result of the shortage.
- 81% of respondents stated they have observed price fluctuations resulting in higher drug acquisition costs as a result of drug shortages.
- 78% of respondents stated that due to drug shortages patients have to go without taking their medication(s).
- 62% of respondents stated that the Pharmacy Benefit Manager (PBM) reimbursements were not reflecting the acquisition cost increases that resulted from drug shortages.
- 52% of respondents stated that insurance companies do not cover alternative therapies and the patient is burdened with the responsibility of paying cash.
- 56% of respondents stated that more than 6 prescriptions per week for ADHD drugs could not be filled due to unavailability.
- 50% of respondents stated that an average of six customers or more per week attempted filling an ADHD prescription at another pharmacy before trying their pharmacy.

Survey Results

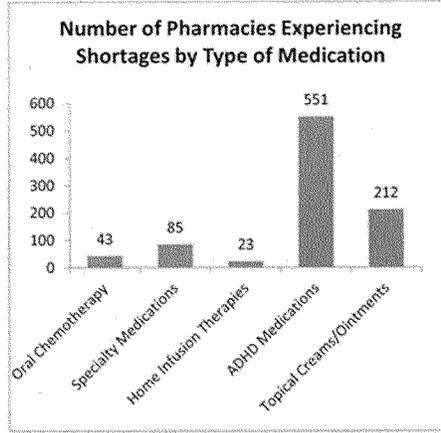
1. In what state is your pharmacy located?



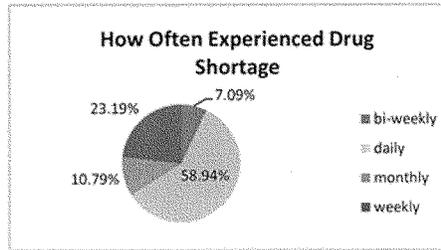
2. Over the past six months, has your pharmacy experienced a drug shortage?



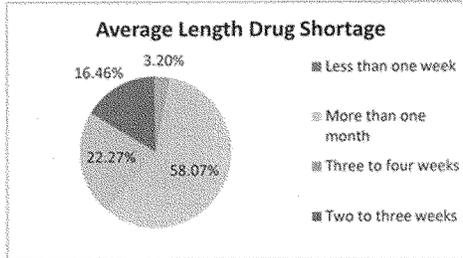
3. What types of medicines have you experienced shortages within the past six months?



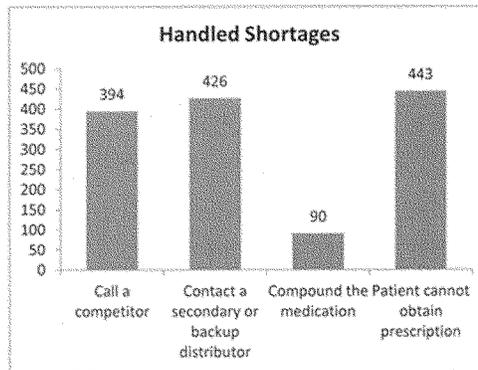
4. Over the past six months, how often have you experienced these shortages?



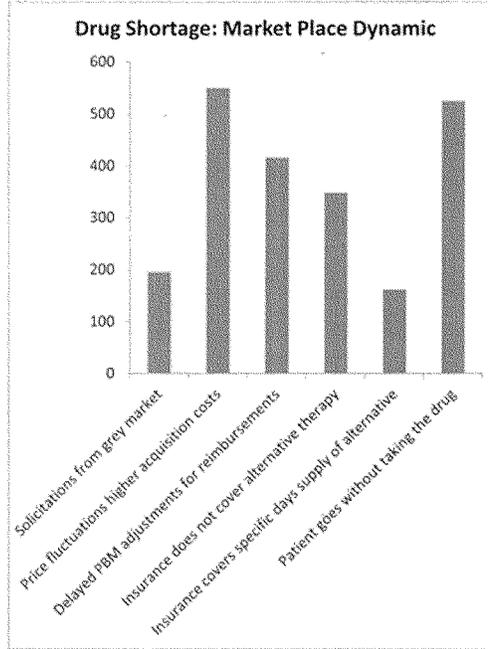
5. If you have experienced a drug shortage over the six months, what is the average length of the duration?



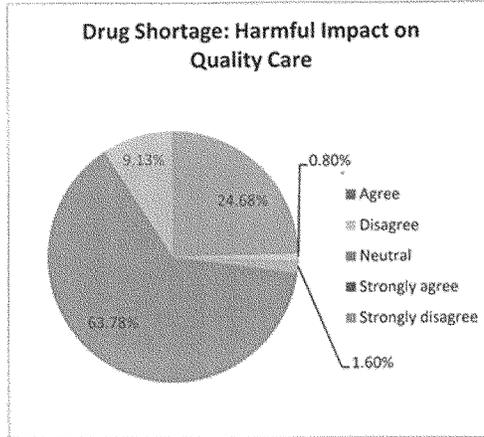
6. How have you handled these shortages?



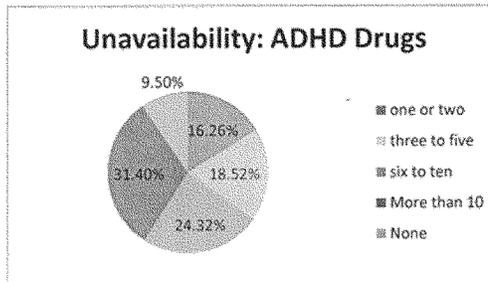
7. Which of the following have you observed during a drug shortage related to marketplace dynamics?



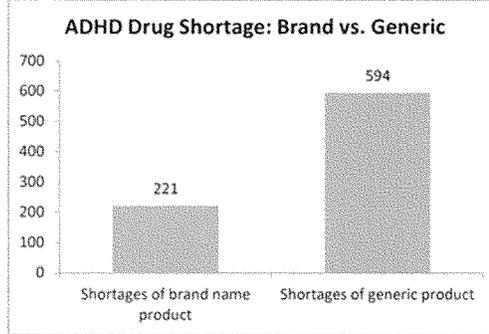
8. I am concerned that the drug shortages I have experienced will have a harmful impact on the quality of care of my patients:



9. During the last 90 days, how many prescriptions for ADHD drugs could not be filled due to unavailability (average number per week):

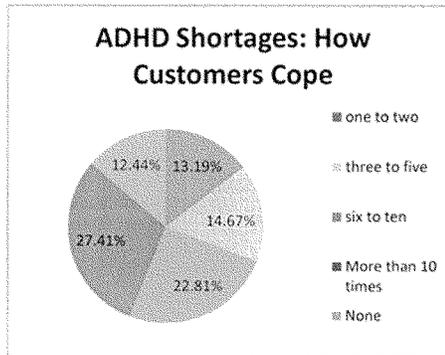


10. If you are experiencing shortages of ADHD drugs, which of the following apply?

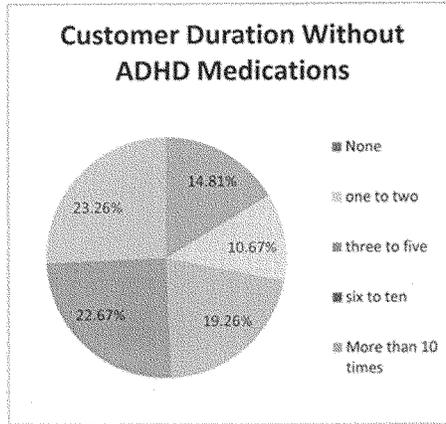


During the last 90 days how many times have you heard the following from your customers regarding shortages of ADHD medications (average number per week)?

11. I've tried to get my/my family member's prescription filled at other pharmacies before coming here.



12. I've been out of my/my family member's medication for more than 24 hours:





NCPA Drug Shortages Survey Results January 2012

Drug shortages are not just impacting hospitals and health system pharmacies; community pharmacies are increasingly facing drug shortage problems as well.

NCPA surveyed our members in January 2012 regarding drug shortages and received a total of 675 responses. These survey results provide important information about drug shortages in the independent community pharmacy setting, which dispenses nearly 40% of all retail prescriptions. Drug shortages have resulted in pharmacies' scrambling to obtain a dwindling supply, an inability to fill prescriptions, higher acquisition costs, a lack of patient insurance coverage for alternative drugs, and more, all of which may result in the patient going without their necessary medications. Ultimately, drug shortages negatively affect patients and the pharmacists' ability to provide patient care.

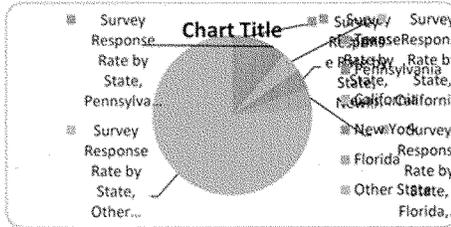
The survey contained specific questions related to shortages of drugs used to treat attention-deficit hyperactivity disorder (ADHD), as this class of medications has been associated with increased scrutiny related to shortages.

Key Highlights

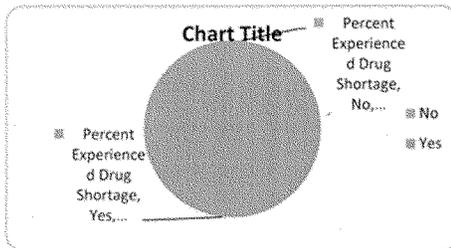
- 96% of respondents have experienced a drug shortage in the past six months.
- 82% of respondents stated that they experienced a shortage of ADHD medications in the past six months – 88% of which were generic drugs – followed by topical creams/ointments (31%) and specialty medications (13%).
- 59% of respondents stated that over the past six months, they have been experiencing drug shortages daily, whereas 23% have been experiencing drug shortages weekly.
- 58% of respondents stated the average length of a drug shortage is more than a month, whereas 22% stated drug shortages last an average of three to four weeks.
- 66% of respondents stated that patients go without their prescription being filled at their pharmacy as a result of the shortage.
- 81% of respondents stated they have observed price fluctuations resulting in higher drug acquisition costs as a result of drug shortages.
- 78% of respondents stated that due to drug shortages patients have to go without taking their medication(s).
- 62% of respondents stated that the Pharmacy Benefit Manager (PBM) reimbursements were not reflecting the acquisition cost increases that resulted from drug shortages.
- 52% of respondents stated that insurance companies do not cover alternative therapies and the patient is burdened with the responsibility of paying cash.
- 56% of respondents stated that more than 6 prescriptions per week for ADHD drugs could not be filled due to unavailability.
- 50% of respondents stated that an average of six customers or more per week attempted filling an ADHD prescription at another pharmacy before trying their pharmacy.

Survey Results

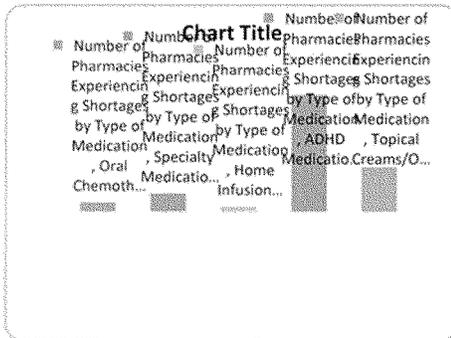
1. In what state is your pharmacy located?



2. Over the past six months, has your pharmacy experienced a drug shortage?

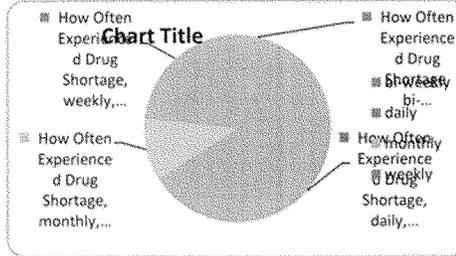


3. What types of medicines have you experienced shortages within the past months?

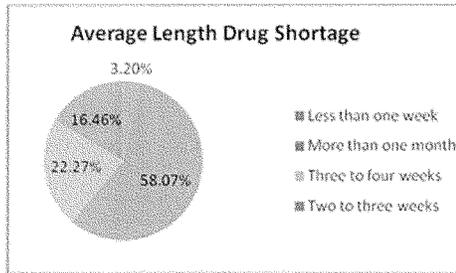


six

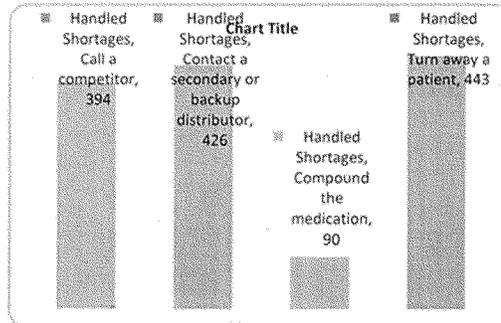
4. Over the past six months, how often have you experienced these shortages?



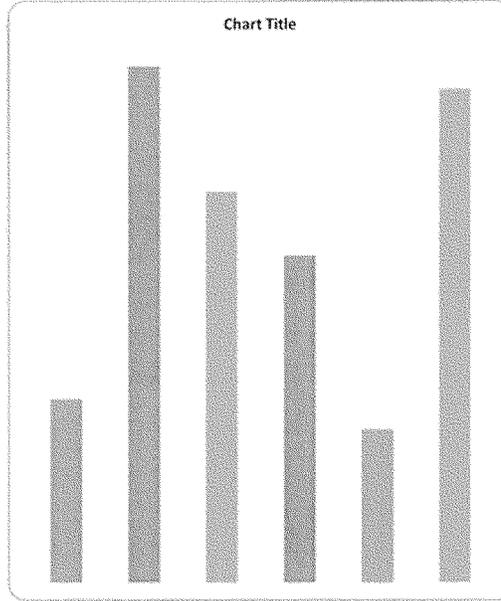
5. If you have experienced a drug shortage over the six months, what is the average length of the duration?



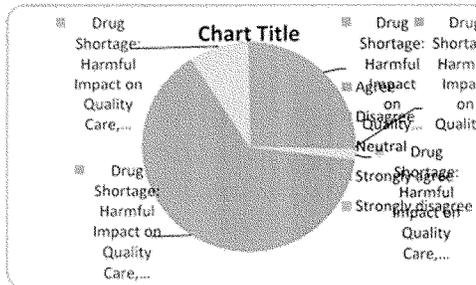
6. How have you handled these shortages?



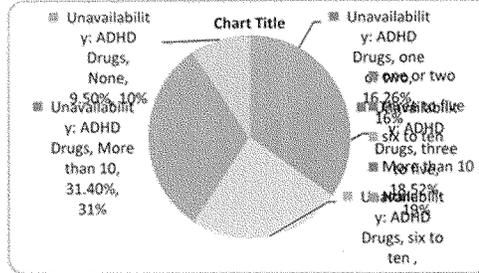
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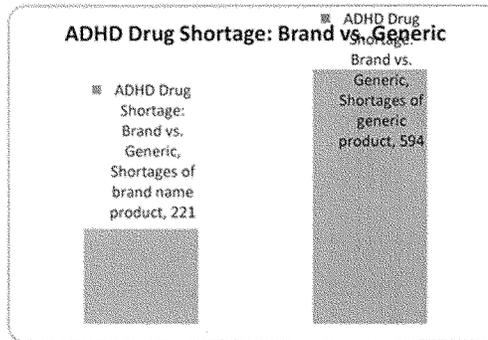
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9. During the last 90 days, how many prescriptions for ADHD drugs could not be filled due to unavailability (average number per week):

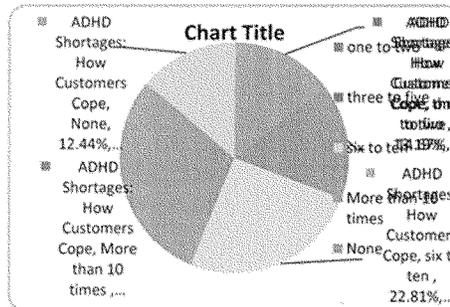


10. If you are experiencing shortages of ADHD drugs, which of the following apply?

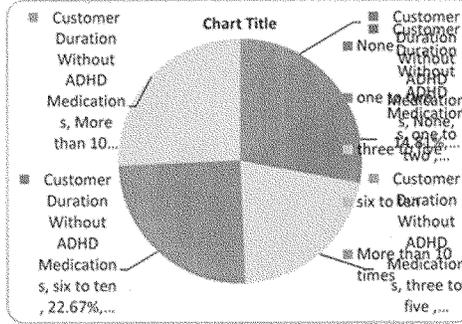


During the last 90 days how many times have you heard the following from your customers regarding shortages of ADHD medications (average number per week)?

11. I've tried to get my/my family member's prescription filled at other pharmacies before coming here.



12. I've been out of my/my family member's medication for more than 24 hours:





STATEMENT OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION (BIO)
HOUSE COMMITTEE ON ENERGY & COMMERCE, SUBCOMMITTEE ON HEALTH
HEARING ON, "THE REVIEW OF THE PROPOSED GENERIC DRUG AND
BIOSIMILARS USER FEES AND FURTHER EXAMINATION OF DRUG SHORTAGES."
FEBRUARY 7, 2012

Chairmen Upton and Pitts, and Ranking Members Waxman and Pallone, the Biotechnology Industry Organization (BIO) thanks you for the opportunity to submit testimony for the record on the House Energy and Commerce, Subcommittee on Health hearing on "The Review of the Proposed Generic Drug and Biosimilars User Fees and Further Examination of Drug Shortages."

BIO SUPPORTS PASSAGE OF THE BIOSIMILARS USER FEE PROGRAM

BIO supports FDA's ongoing implementation of a well-constructed, science-based pathway for the approval of biosimilar products. A transparent, predictable, and balanced regulatory framework for the review and approval of biosimilars accompanied by reasonable performance goals and a dedicated, independent funding stream will ensure that FDA can facilitate the development and evaluation of biosimilars products, while also continuing to prioritize the review of innovative drugs and biologics so that safe and effective new treatments – many for currently untreatable and serious diseases – can be made readily available to patients.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

Throughout both the legislative consideration of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) and ongoing FDA implementation of the pathway, BIO has articulated several key principles that will promote the development of an effective regulatory framework for biosimilar products:

- Ensuring Patient Safety
- Recognizing Scientific Differences Between Drugs and Biologics
- Maintaining the Physician-Patient Relationship
- Preserving Incentives for Innovation

- Ensuring Transparent Statutory and Regulatory Processes
- Continuing to Prioritize FDA Review and Approval of New Therapies and Cures

BIO believes that the proposed user fee program is consistent with these principles and supports Congressional authorization of the program.

FDA's Biosimilars Activities Should be Supported by a Dedicated and Independent Source of User Fees

The establishment of a stand-alone, independent biosimilars user fee program is consistent with Congressional intent and precedent established under other user fee programs. BIO recognizes that 351(k) applications will raise novel and complex questions of science and law, requiring substantial time, expertise, and additional resources to ensure a thorough regulatory review. BIO believes that one of the principal goals of this new user fee program must be to ensure that workload associated with biosimilar applications does not harm the Agency's ability to efficiently review innovative drugs and biologics, and that new treatments continue to have the highest review priority. Accordingly, we agree with FDA's principle that the Agency needs sufficient review capacity and dedicated user fee resources for 351(k) applications to assure that resources are not redirected from innovator reviews.

User Fees should be Complemented by a Sound Base of Appropriations

Additionally, BIO recognizes that, historically, most FDA user fee programs have been established on a pre-existing base of appropriations. However, given the recent establishment of the biosimilars program at FDA, only modest appropriations are currently allocated to the program, which are inadequate to meet the anticipated workload demands. To facilitate an equitable balance of fees and appropriations, FDA and industry support a trigger provision - similar to the established appropriations triggers in other user fee programs - that would ensure that FDA allocates at least \$20 million per year to the program. BIO encourages Congress to recognize the importance of a well-resourced and viable biosimilars pathway at FDA and we request that adequate new funding be appropriated for the program.

Biosimilar Product Development Fees are a Necessary, but Provisional Measure:

The biosimilars user fee program also establishes a unique biosimilar product development fee, which is ultimately deducted from the sponsor's application fee. Since there is no established biosimilars industry, facility base, and product base to form a stable funding source for activities that occur before submission of applications, it is important to "front-load" the fees through the product development fee so that the agency has available resources to meet with sponsors during development to provide scientific advice and feedback. It should be noted, however, that the assessment of a product development fee is unique to this situation with respect to biosimilar products and should not establish any precedent for IND fees under the Prescription Drug User

Fee Act (PDUFA) program. Additionally, any IND-associated fee should sunset permanently in FY 2018 when both PDUFA and this new user fee program would sunset.

In conclusion, BIO supports enactment of the proposed biosimilars user fee program, which will provide FDA with adequate resources and promote predictability in FDA's biosimilars review process, while continuing to promote the development and evaluation of innovative therapies for unmet medical needs.

DRUG SHORTAGES

In recent years, the FDA has documented a significant increase in the prevalence of prescription drug shortages. These shortages can create significant concerns for patients seeking to maintain a treatment regime for their disease or condition and can even delay or halt clinical trials necessary to bring new therapies to market. The biotechnology industry is committed to the discovery and development of new, novel treatments for serious and life-threatening diseases, and the premise that drug shortages are preventing patient access to needed treatments stands counter to our driving mission to extend and enhance the lives of patients.

I. The Multi-Faceted Factors Contributing to Drug Shortage

The factors contributing to drug shortages are complex and multi-faceted, and the economic, logistical, and scientific factors can vary significantly among different sectors of the pharmaceutical industry, including branded and generic manufacturers. Consequently, there is no one-size-fits all solution to this issue and each individual contributing factor must be critically evaluated. Recent studies and public workshops have cited a number of contributing factors to drug shortages, including:^{1, 2, 3}

- Unanticipated shifts in market demand, clinical guidelines, or the practice of medicine
- Manufacturing production and quality problems
- Limited manufacturing capacity
- Delays in site consolidation and facility modernization
- Disruptions in ingredient supplies
- Regulatory actions, including recalls, inspections and changes in compliance requirements, delayed new drug approvals, and delays in approval of facility upgrades
- Industry consolidation, product discontinuations, and economic factors
- Just-in time supply chain with short inventory management

¹ Hill and Reilly, American Society of Health System Pharmacists, *Can the United States Ensure an Adequate Supply of Critical Medications?*, Food and Drug Law Institute Policy Forum, Volume 1, Issue 16, August 24, 2011, <http://www.fdlr.org/pubs/policyforum/>.

² Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), *Approach to Addressing Drug Shortage: Public Workshop*, September 26, 2011, <http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm>.

³ U.S. Government Accountability Office. (2011, September). *Manufacturer Discounts in the 340B Program Offer Benefits, but Federal Oversight Needs Improvement*. Publication No. GAO-11-836. <http://www.gao.gov/new.items/d11836.pdf>

According to FDA, sterile injectables accounted for 74% of the drug shortages reported to the Agency in 2010. Critical shortages are most acute for off-patent sterile injectable products, including certain chemotherapy agents, total parenteral nutrition (TPN) electrolytes, and anesthetics. Of the sterile injectables reported in short supply in 2010, 54% of the shortages were caused by product quality or current Good Manufacturing Practice (cGMP) issues, 21% were caused by manufacturing capacity issues or delays, and 11% were caused by product discontinuations.⁴

II. Approaches to Resolve Drug Shortages

In the experience of many biotechnology companies, FDA staff work constructively and collaboratively with the manufacturer in the event of a shortage to help resolve the problem and restore patient access to needed therapies as soon as possible. However, there are several steps that Congress can take to help further bolster the capacity of FDA and manufacturers to prevent and respond to drug shortages. We recognize that FDA has limited staff and resources to direct to these activities, and BIO has long supported the efforts of the *Alliance for a Stronger FDA* to secure additional appropriated funding to help mitigate drug shortages and implement the proposals below.

- **Expedited FDA Review of Manufacturing Supplements:** Some shortages may be caused when manufacturers are upgrading manufacturing facilities, but the supplement requesting approval from FDA has not been approved in a timely manner or has undergone multiple review cycles. Expedited review of these regulatory submissions may contribute to resolving the shortage.
- **Prioritized Reinspections of Facilities:** To the extent that a reinspection can help to resolve a prior adverse inspectional finding and bring a facility back online, FDA should strive to prioritize reinspections for facilities related to a shortage. It is extremely important that the FDA is adequately resourced to be able to prioritize post-market drug shortage related reinspections while at the same time continuing to meet its pre-market PDUFA inspectional commitments.
- **Joint and Harmonized Inspections:** Leveraging resources among established regulatory authorities to conduct joint inspections may also help to expedite inspections. We also encourage regulatory authorities to internationally harmonize standards for compliance inspections to minimize inconsistency between inspectorates, and even between individual inspectors.
- **Faster Review of New Drugs:** Occasionally, a new drug or efficacy supplement can help to resolve an existing drug shortage. However, FDA has not consistently met its drug and biologic review goals in the recent past. Swift passage of PDUFA V - which establishes a new review process for new molecular entities (NMEs) aimed at facilitating timely availability of new drugs – will help to alleviate drug shortages in certain situations.
- **FDA Guidance on Continuity of Supply Chains and Risk Mitigation:** To help ensure that all manufacturers have firm knowledge of suppliers and adopt best practices to help

⁴ Food and Drug Administration, “Webinar on Prescription Drug Shortages”, September 30, 2011, <http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM273360.pdf>.

mitigate the risk in the upstream supply chain, we suggest that FDA issue guidance for industry. Voluntary and coordinated information sharing between stakeholders regarding the quality and authenticity of supply and suppliers and information on counterfeits, cargo thefts and adulterated product can help to identify and mitigate potential supply chain disruptions and vulnerabilities before they manifest into a drug shortage.

BIO looks forward to working with the Committee to find practical ways to resolve the drug shortage issue. Thank you.

References:

- i Food and Drug Administration. "Webinar on Prescription Drug Shortages", September 30, 2011, <http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM273360.pdf>.
 - ii Hill and Reilly, American Society of Health System Pharmacists. *Can the United States Ensure an Adequate Supply of Critical Medications?*, Food and Drug Law Institute Policy Forum, Volume 1, Issue 16, August 24, 2011, <http://www.fdi.org/pubs/policyforum/>.
 - iii Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), *Approach to Addressing Drug Shortage; Public Workshop*, September 26, 2011, <http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm>.
 - iv U.S. Government Accountability Office. (2011, September). *Manufacturer Discounts in the 340B Program Offer Benefits, but Federal Oversight Needs Improvement*. Publication No. GAO-11-836. <http://www.gao.gov/new.items/d11836.pdf>
 - v Food and Drug Administration, "Webinar on Prescription Drug Shortages", September 30, 2011, <http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM273360.pdf>.
 - vi FDA Center for Drug Evaluation and Research, *Current Drug Shortages*, <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm>, (accessed October 17, 2011)
 - vii FDA Center for Biologics Evaluation and Research, *Biologic Drug Shortages*, <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm>, (accessed October 17, 2011)
 - viii Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product Is \$1.2 Billion. According to the Tufts Center for the Study of Drug Development," November 9, 2006. www.csdd.tufts.edu.
- Notification Requirements:** Reasonable, clear, and collaborative processes for Sponsors to notify FDA of a drug shortage may help to mitigate the shortage and restore patient access to therapies.

Mr. PITTS. All right. The Chair will call panel two to the table and would like to thank you all for agreeing to testify before the subcommittee today. And I would like to quickly introduce our panel. First, Ms. Heather Bresch is the CEO of Mylan, Inc; second, Mr. David Gaugh is the vice president of regulatory sciences at the Generic Pharmaceutical Association; and Dr. Bill Greene is the chief pharmaceutical officer at St. Jude Children's Research Hospital. Again, thank you all for coming. We have your prepared statements which will be entered in the record and we ask you to summarize your opening statement 5 minutes.

Ms. Bresch, we will begin with you. You are recognized for 5 minutes to summarize your testimony.

STATEMENTS OF HEATHER BRESCH, CHIEF EXECUTIVE OFFICER, MYLAN, INC.; DAVID GAUGH, VICE PRESIDENT, REGULATORY SCIENCES, GENERIC PHARMACEUTICAL ASSOCIATION; AND BILL GREENE, PHARM.D, BCPS, FASHP, CHIEF PHARMACEUTICAL OFFICER, PHARMACEUTICAL SERVICES, MEMBER, PHARMACEUTICAL SCIENCES, ST. JUDE CHILDREN'S RESEARCH HOSPITAL

STATEMENT OF HEATHER BRESCH

Ms. BRESCH. Thank you and good morning, Chairman Pitts and Ranking Member Pallone and members of the subcommittee, and thank you for the opportunity to testify today.

I am Heather Bresch, CEO of Mylan, Inc., the largest global generics company in the world headquartered in the United States. Mylan was founded 50 years ago in West Virginia, and for the first 45 years of our history, Mylan was a domestic company that served the U.S. market. In 2007, we transformed into a global company. Today, we provide products in more than 150 countries, have a global workforce of more than 18,000, including more than 5,000 employees in the United States. Our largest drug manufacturing facility is located in Morgantown, West Virginia, where we produce nearly 20 billion doses of medicine each year. We also have multiple facilities outside of the U.S. that produce drugs that are distributed in this country and which are inspected by the FDA. Today, 1 out of every 11 prescriptions dispensed in the United States is a Mylan product. In light of our success in the global market, Mylan is adding manufacturing jobs around the globe, and we would like to not only maintain what we already have here in the United States, but we would also like to expand our U.S. presence.

As we transform from a domestic to a global company, we were surprised to discover that FDA is still operating as a domestic agency and is not equipped with the resources or legal authority to regulate the now global drug industry that serves the United States. In fact, FDA is governed by a 1938 law, which has been largely unchanged since its initial passage and does not give FDA the full authority it needs to oversee the global industry.

Unfortunately, the 1938 law also creates an unlevel playing field for American manufacturers by requiring U.S. manufacturers to be inspected every 2 years while the law is silent on foreign drug manufacturers. As a result, two standards are created—one for the United States' manufacturers and one for foreign. U.S. manufactur-

ers actually have a perverse incentive to move existing U.S. jobs abroad where they will face less regulatory scrutiny and also can avoid the second-highest combined Federal/State corporate tax rate of 39 percent.

As the Pew Health Group reported to this subcommittee last week, complying with quality systems and FDA regulations represents approximately 25 percent of a drug manufacturer's operating cost. This disparity in standards raises very real and profound questions about the integrity and quality of the drug supply in the U.S. Clearly, every consumer should have the peace of mind of knowing that every drug product dispensed in the U.S. is held to the same standard of quality regardless of whether the product originated in the United States or outside of its borders.

Over the last several years, the number of foreign facilities supplying the U.S. has grown by 185 percent, while at the same time, FDA inspection rates have decreased by nearly 57 percent according to the FDA. FDA estimates that up to 40 percent of drugs now consumed by U.S. patients are manufactured abroad and 80 percent of the active ingredients used in drugs come from foreign countries.

The growth in the number of foreign facilities coupled with a significant increase in generic drug application has caused FDA's workload to be far outpaced by its resources, and as a result, the time it takes to get a generic drug approved has nearly doubled with more than 2,700 generic applications awaiting approval from FDA today. Now more than ever Americans need more timely access to more affordable generic medicine which has saved patients and the government more than 930 billion in the last decade alone.

With a 50-year history of working closely with Congress and the FDA, Mylan is pleased that the generic industry has stepped up first and addressed an industry-wide issue impacting brand and generics to help address FDA's challenge of carrying out its mission within a global industry, especially given the current scarcity of government resources.

The landmark and novel user fee program is aimed at three critical components: safety, access, and transparency. Through GDUFA, FDA will receive approximately 1.5 billion in new funding over the next 5 years, and in return, FDA has agreed to more timely reviews of generic drug applications, increased transparency, and by any old good manufacturing practice surveillance inspections of all generic finish dosage form and active pharmaceutical ingredient manufacturers, foreign and domestic, on a risk-adjusted basis, among other benefits outlined in a negotiated goals letter.

Strengthening the supply chain, a key aim of GDUFA through routine GMP inspections for all facilities, as well as transparency initiatives that require the identification and registration of facilities involved in the supply chain will also provide a more holistic solution to current drug shortages. Additionally, decreased review times will ensure more timely access to new generic products, including those that addressed an unmet medical need or those in short supply.

While the generic industry and API industries will help provide the financial resources to globalize the FDA, it is imperative for Congress to update the 1938 law to ensure the integrity of the sup-

ply chain and a level playing field so companies like Mylan are not disadvantaged to grow American manufacturing jobs. A level playing field will also benefit foreign facilities as well as small and first-time entrants who are currently disadvantaged by delays in new product approvals because of a lack of a recent inspection.

We urge Congress to adopt GDUFA as negotiated and move forward in updating the 1938 law. Only by taking these steps can we provide more timely access to more affordable generics, ensure competitiveness by leveling the playing field for American manufacturers, and equip FDA with the authority it needs to become a global agency to ensure the integrity of the global drug supply chain.

Thank you. And I would be happy to address any questions of the committee.

[The prepared statement of Ms. Bresch follows:]



TESTIMONY OF

HEATHER BRESCH

CHIEF EXECUTIVE OFFICER

MYLAN INC.

**REVIEW OF THE PROPOSED GENERIC DRUG AND BIOSIMILARS USER FEES AND
FURTHER EXAMINATION OF DRUG SHORTAGES**

BEFORE THE

COMMITTEE ON ENERGY & COMMERCE

SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

FEBRUARY 9, 2012

**"Review of the Proposed Generic Drug and Biosimilars User Fees
and Further Examination of Drug Shortages" – February 9, 2012**

**Summary of Testimony before the House Energy and Commerce Committee, Subcommittee on Health
Heather Bresch, CEO, Mylan Inc.**

When FDA was essentially created through the FDCA of 1938, FDA was equipped as a domestic agency charged with overseeing a domestic industry. Today, the drug industry supplying the U.S. is a global one, but FDA still remains domestic. Congress should update the FDCA of 1938 to equip FDA as a global agency to strengthen the integrity of the supply chain and ensure a level playing field for manufacturers.

- **Current Landscape For Generic Drugs.** Now more than ever, Americans and the government need more timely access to low cost, high quality medicine. The generic drug industry has saved the government, patients and payors more than \$931 billion over the last decade alone by reliably providing low cost, safe and effective generic drugs. Recent years have seen a significant increase in the number of applications for generic products, as well as substantial growth in the foreign facilities that support the U.S. drug supply. Unfortunately, FDA's resources have not kept up with this increased workload, and, as a result, the time it takes to get a generic drug approved has nearly doubled in recent years and more than 2,700 applications are currently awaiting FDA approval. Because a recent inspection history is required prior to product approval, the inspection backlog is likewise adding to the long delays in generic approvals.
- **Landmark Generic Drug User Fee Program.** To help provide FDA with supplemental resources to address the challenges caused by globalization of the drug supply chain and the related increase in the agency's workload, the generic drug industry negotiated a landmark generic user fee program ("GDUFA") that provides \$299 million annually and is focused on three key aims: **1) Safety** – ensuring that both foreign and domestic industry participants in the U.S. generic drug system are held to the same, consistent, high quality standards and are GMP inspected by FDA biennially using a risk-based approach; **2) Access** – expediting the availability of generic drugs through more timely reviews; and **3) Transparency** – Enhancing FDA's ability to require the identification and registration of all facilities involved in the manufacture of generic drugs.
- **More timely access to Generics Expected to Increase Savings and Lower Health Care Spend.** Generics currently save the government and consumers more than \$3 billion each week. GDUFA will provide more timely access to more affordable generics, which is expected to even further lower government and consumer health care spending.
- **Supply Chain Integrity.** One of the key ways FDA oversees continued compliance with the quality standards required of all prescription drugs sold in the U.S. (branded and generic) is by conducting on-site GMP facility inspections. These critical surveillance inspections (known as GMP inspections) ensure that facilities are continuing to meet their obligation of producing safe products in accordance with rigorous current good manufacturing practices and are intended, among other things, to identify potential concerns or observations before an issue emerges or increases in severity so as to later interrupt or impact the safety or efficacy of the drug supply.
- **Pressing Need to Globalize FDA Authority.** Today, 40% of all drugs Americans take are imported and up to 80% of the active pharmaceutical ingredients in those drugs come from foreign facilities. FDA's GMP inspections have not kept pace with the exponential growth in foreign facilities that supply the U.S. pharmaceutical market. According to FDA, foreign facilities supporting the U.S. drug supply have grown by 185% while at the same time FDA inspection rates have decreased by nearly 57%. Moreover, the Federal Food, Drug and Cosmetic Act of 1938 ("FDCA") requires American manufacturers associated with pharmaceutical production to undergo a GMP inspection every two years but the law does not require the same of foreign manufacturers, which are inspected every nine years on average.
- **Unlevel Playing Field Decreases Competitiveness.** The inspection disparity between foreign and domestic manufacturers disadvantages U.S. companies by creating an unlevel playing field that encourages the export of U.S. jobs and holds U.S. manufacturers to higher standards with associated higher costs. Pew reports that it costs 25% more to maintain facilities in compliance with GMP.
- **Delayed Entry of New Generic Drugs.** The infrequency of foreign facility inspections delays approval of new medicines, including generics. The inspection disparity also disadvantages generic drug applicants, particularly foreign applicants as well as small and first time entrants who are delayed in obtaining approvals for new products due to a lack of a recent inspection history which is required for approval.
- **Authority Needed to Modernize FDCA.** The generic drug industry, which represents 78% of the U.S. drug supply, will provide FDA with most of the supplemental resources it needs to conduct biennial GMP inspections on a risk-adjusted basis under GDUFA. We urge Congress to update the FDCA to give FDA the legal authority it needs to level the playing field for inspection parity and ensure FDA is equipped by law to carry out its mission in overseeing a global drug supply chain.
- **Drug Shortages.** An important benefit of GDUFA is that potential weak links in the supply chain can be identified and addressed as early as possible through routine GMP surveillance inspection to prevent supply disruptions. GDUFA's decreased review times will ensure more timely access to new generic products, including those that address an unmet medical need or those in short supply.
- **Biosimilar User Fees.** User fees for biologics have been developed in accordance with the mandate provided under the Affordable Care Act. However, much work beyond user fees remains to be done to develop a workable pathway that generates the expected savings to Americans and provides access to more affordable generics.

I. INTRODUCTION

Good morning Chairman Pitts, Ranking Member Pallone, and members of the Subcommittee. Thank you for the opportunity to testify today on the Generic Drug User Fee Act program ("GDUFA"), which is jointly proposed by the U.S. Food and Drug Administration ("FDA") and industry, the Biosimilars User Fee Act ("BsUFA"), and the committee's examination of the issues surrounding drug shortages.

I am Heather Bresch, CEO of Mylan Inc., the world's third largest generic and specialty pharmaceutical company and the largest global generics company headquartered in the United States. I also serve on Mylan's board of directors. I have spent 20 years at Mylan, holding numerous positions across more than 15 areas of our business. Prior to becoming CEO, I served as president, where I was responsible for the day-to-day operations of the company. Before that, I served as Mylan's chief operating officer and chief integration officer, leading the successful integration of two transformational international acquisitions – Matrix Laboratories and Merck KGaA's generics business. In addition, I served as head of Mylan's North America operations. I also served two consecutive terms as chairman of the Generic Pharmaceutical Association and one term as its vice chairman. Over the course of my career, I have been a strong advocate of initiatives and policy changes aimed at removing barriers that hinder patient access to high-quality medicine.

II. BACKGROUND

Mylan was founded 50 years ago in White Sulphur Springs, West Virginia and for the first 45 years of our history, Mylan only served the U.S. market. Realizing that we would need to expand our footprint to produce the needed scale and reliable quantities of high quality medicine to compete in our now global drug industry, Mylan has now transformed from a purely domestic company into a global one over the last five years.

Today, we provide products to customers in more than 150 countries and territories and have a global workforce of more than 18,000, including over 5,000 employees in the U.S. We maintain one of the industry's broadest and highest quality product portfolios, with more than 1,000 separate products across more than 20 disease states, supported by a robust product pipeline.

We also operate one of the world's largest active pharmaceutical ingredient manufacturers, and run a specialty pharmaceuticals business focused on respiratory, allergy and psychiatric therapies. Today, one out of every 11 prescriptions dispensed in the United States, brand or generic, is a Mylan product. In addition to our multiple U.S. facilities, including our largest facility in Morgantown, West Virginia which produces nearly 20 billion doses of medicine on average each year, Mylan now has multiple facilities outside the U.S. that supply the U.S. market. All of our facilities that supply the US market have been inspected and measured by the same high quality standards of FDA.

We are proud of the investments we make in all of our facilities around the world to deliver quality products. We also are proud of our role in providing

patients with access to more affordable medicine, particularly here in the United States, where the generic drug industry has collectively provided more than \$931 billion of savings over the last decade as a result of the use of high quality generic prescription drugs in place of brand name counterparts.¹ Today, 78% of all prescriptions dispensed in the United States are generics.

As we have expanded our domestic based structure to reflect our now global footprint, Mylan quickly discovered that while we and much of our industry are now global, FDA is still effectively operating as a domestic agency that is not equipped with the resources or legal authority to regulate the global drug supply that now serves the U.S. market. Indeed, FDA is governed by an antiquated law, the Federal Food, Drug and Cosmetic Act ("FDCA"), key sections of which have not been updated since its passage in 1938 when the U.S. operated almost entirely as a domestic pharmaceutical market. As currently written, the FDCA does not properly equip FDA with the authority it needs to carry out its mission in the now globalized U.S. pharmaceutical supply chain. For example, current law requires that U.S.-based manufacturers be inspected by FDA every two years, but does not require the same of foreign manufacturers.

We also discovered that FDA resources have been far outpaced by a significant increase in workload, generated by a dramatic increase in abbreviated new drug applications and exponential growth in foreign facilities supplying the U.S. pharmaceutical market. Given that FDA operates under a legal requirement to inspect U.S. facilities bi-annually and that the law is silent on foreign facilities,

¹ "An Economic Analysis of Generic Drug Usage in the U.S." Independent Analysis by IMS Health, Sept. 2011.

FDA has deployed the vast majority of its resources domestically. The end result is an unlevel playing field for U.S. manufacturers, different quality standards for products sold in the U.S. based on where they were manufactured, and a significant delay in FDA review times of generic drug applications, with a backlog of more than 2,700 abbreviated new drug applications, and many awaiting a recent inspection history before approval can be granted.

Just as the pharmaceutical industry has transformed into a global one, in order to meet its mission, so too must FDA. To that end, with a 50-year history of working closely with the FDA, Mylan is pleased to have played a leading role in developing and negotiating a comprehensive user fee program for generic drugs, along with our colleagues across the generic and API industries.² The GDUFA program helps address FDA's challenge of carrying out its mission in the face of a global drug supply chain and providing patients with more timely access to more affordable, safe and effective medicine.

GDUFA recognizes that while providing earlier access to effective medicines is critical (the key aim of all other existing user fee programs), an equally important pillar of FDA's mission is ensuring the safety and integrity of the drug supply. As a result, in addition to expediting access to more affordable, high quality generic drugs, the key goals of the Generic Drug User Fee Program described further below include holding all industry participants contributing to

² See Mylan Inc. Submissions to Docket No. FDA-2010-N-0381 proposing a holistic user fee program dated October 17, 2010 and Testimony before FDA to discuss generic drug user fees, September 17, 2010. See also Matrix Laboratories Limited (subsidiary of Mylan Inc.) Submission to Docket No. FDA-2010-N-0381 dated March 30, 2011.

the U.S. generic drug system, foreign and domestic, to the same rigorous GMP inspection standards and enhancing FDA's ability to identify, track and register all facilities involved in each generic drug sold in the U.S.³

Through GDUFA, the generic industry, which as I noted represents more than three fourths of all prescriptions dispensed in the U.S., will provide FDA with approximately \$1.5 billion in new funding over the next five years. In return, FDA has agreed to more timely review of generic drug applications (i.e., by year 5 of the program, 90% of abbreviated new drug applications ("ANDAs") will be at 10-month complete review times), increased transparency, and biennial GMP surveillance inspections of all generic finished dosage form ("FDF") and active pharmaceutical ingredient manufacturers ("API") – foreign and domestic – on a risk adjusted basis.⁴

However, while this funding will help FDA make significant progress in addressing critical industry-wide issues, there is more that Congress can do to help address the issue of supply chain integrity. In order to truly eliminate the disparity between foreign and domestic facility inspection rates, create a more level playing field for U.S. manufacturers, and better ensure the safety of the global supply chain, we join the Generic Pharmaceutical Association ("GPhA") in

³ Although GDUFA requires FDF and API manufacturers to both pay respective fees and register as part of the generic drug user fee program, GDUFA requires all other generic drug program participants to register even though such participants are not responsible for a fee through Sept. 31, 2017 under GDUFA.

⁴ See GDUFA goals letter for further explanation of risk basis. See also GPhA's testimony before the Senate HELP Committee, dated Sept. 17, 2011. (A "risk-based" model for inspections prioritizes inspections according to a company's safety and compliance track record. This system would ensure that questionable or problematic facilities receive a comprehensive review and evaluation sooner. Facilities with strong records of compliance and positive inspections would be placed further down on the inspection schedule, allowing the agency to prioritize its immediate attention on companies that have never had an inspection or that have a history of compliance issues.)

urging Congress to amend the FDCA to reflect the inspection model being established by GDUFA, thus modernizing FDA's existing authority to reflect the needs of the current 21st century global drug supply.

As part of a Special Report issued by FDA in July 2011, entitled *Pathway to Global Product Safety and Quality*, FDA outlined its plan to "transform itself from a domestic agency operating in a globalized world to a truly global agency fully prepared for a regulatory environment in which product safety and quality know no borders." In this report, FDA likewise acknowledged that to carry out its mission in the globalized pharmaceutical market, the agency is "looking to Congress to modernize its antiquated authorities so that FDA's legal tools keep pace with globalization."⁵

III. KEY ISSUES THAT A DOMESTICALLY FOCUSED FDA FACES IN CARRYING OUT ITS MISSION IN A GLOBAL DRUG SUPPLY

A. Challenges caused by global drug supply chain

With a mission to protect and promote the public health, FDA has a critical responsibility, along with industry, to ensure the safety, efficacy and security of the U.S. drug supply. Fulfilling this responsibility today is much more challenging than it was in 1938, when the FDCA was enacted. Back then, most of the pharmaceutical products consumed in the U.S. were produced in the U.S. Today's U.S. pharmaceutical industry is global, highly complex and growing rapidly, considerably outstripping the agency's operating capacity.

Drug products, both branded and generic, originate in factories all over the world, moving into the American marketplace through supply chains that can

⁵ FDA, Special Report, *Pathway to Global Product Safety and Quality*, page 4. (July 2011)

involve numerous processing plants, manufacturers, suppliers, brokers, packagers and distributors. The agency estimates that up to 40 percent of finished drugs consumed by U.S. patients are manufactured abroad and 80 percent of the active ingredients and bulk chemicals used in drugs come from foreign countries.⁶ According to FDA, the number of foreign drug facilities supplying the U.S. has grown by 185 percent between 2001 and 2008 while at the same time FDA inspection rates have decreased by nearly 57 percent.⁷ Further, the number of FDA-regulated products arriving from abroad has grown substantially. In 2010, nearly 20 million shipments of food, drugs and cosmetics arrived at U.S. ports of entry.⁸ A decade earlier, that number was closer to 6 million, and a decade before, just a fraction of that figure.⁹ Today, 20 to 25 cents of every consumer dollar spent in the U.S. is spent on an FDA-regulated product.¹⁰

Despite the globalization of the pharmaceutical supply chain, the U.S. has not modernized the laws governing supply chain integrity or the scope of its regulatory oversight to reflect the reality of the global marketplace. As a consequence, FDA currently has limited de facto oversight of imported drugs, making it effectively impossible to ensure the quality of the nation's drug supply. In addition, FDA's lack of resources threatens the availability of drugs.

⁶ U.S. Government Accountability Office. Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed (Publication No. GAO-10-961). (September 2010).

⁷ Deborah M. Autor, Deputy Commissioner, U.S. Food and Drug Administration, *Ensuring the Safety, Efficacy, and Quality of Drugs*, A Roundtable on Ensuring the Safety of the U.S. Drug Supply, Mar 14-15, 2011.

⁸ Remarks of Margaret A. Hamburg, M.D., Commissioner of Food And Drugs at Center for Strategic and International Studies (February 4, 2010)

⁹ *Id.*

Importantly, American manufacturers are being disadvantaged versus foreign competitors who do not face the same stringent – and costly – manufacturing and quality standards applied to U.S. companies.¹¹ In order to compete in the global marketplace, some U.S. pharmaceutical manufacturers actually have a perverse incentive to move existing U.S. jobs abroad, where they will face less regulatory scrutiny than those manufacturing in the US. These issues will only be addressed through modernization of U.S. law and the provision of resources necessary to fully fund the FDA’s oversight of today’s complex and global drug supply.

IV. THE GENERIC DRUG INDUSTRY HAS STEPPED UP TO THE PLATE TO ADDRESS INDUSTRY WIDE ISSUE

A. Generic Drug User Fee Act (“GDUFA”)

Given the significant challenges FDA faces in carrying out its responsibility, the substantial growth in applications and facilities requiring FDA review and oversight, as well as the need for a recent inspection history before a new product can be approved, the generic user fee program is focused on helping the agency holistically achieve the following key aims:

Safety – Ensuring that generic industry participants, foreign or domestic, who participate in the U.S. generic supply are held to consistent high quality standards and are GMP inspected every two years, using a risk-based approach, with foreign and domestic parity.

¹¹ See *generally*, Pew Health Group, *After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs*.

Access – Expediting consumer access to generic products by improving timeliness in the review process and providing greater predictability to the application review process to encourage additional innovation.

Transparency – Enhancing FDA's ability to protect Americans in the complex global supply environment by identifying and requiring the registration of all facilities involved in each generic product in the U.S., and improving FDA's communications and feedback with industry in order to expedite product access.

Historically, the generic industry has not used a fee program to provide funding to the FDA review process, as the brand drug and medical device industries have. However, as I described, FDA's current resources have not been adequate to manage the expanding workload caused by an increase in both the number of ANDAs and the number of facilities, with the most growth coming from foreign facilities supporting those applications. The FDA has acknowledged that delays in foreign inspections have contributed to delays in generic drug approval times because facilities listed in applications lack a recent inspection history, which is required before a new generic drug application may be approved. Over the last several years, the review and approval time for an ANDA has nearly doubled. Currently, it is estimated that over 2,700 ANDAs are now awaiting FDA review and the average review time for an ANDA is nearing 32 months.

The delay in approval time also undermines the 180-day exclusivity Congress provided under the Hatch-Waxman Act to incentivize companies to take on the substantial litigation risk associated with such patent challenges in

order to get more affordable prescription drugs into the hands of consumers before patents expire. Under current law, if an applicant does not obtain tentative approval of its ANDA within 30 months of filing, that applicant will lose this vital 180-day exclusivity. The original intent of the forfeiture provision, which was written when the average ANDA approval time was at 16 months, was to ensure that ANDA applicants actively worked toward approval. With the average review time now 32 months, the 180-day exclusivity incentive is significantly threatened through no fault of the ANDA filer.¹²

The generic drug user fee program calls for a broad range of participants in the generic drug industry to contribute \$299 million, adjusted annually for inflation, for each of the five years of the program starting October 1, 2012, which will supplement appropriated funds. In order to ensure that patients, payors and the government continue to benefit from the significant savings offered by generic drugs, representing an average of \$3 billion in savings each week, it was imperative to the industry and FDA to design a program that would keep the individual fee amounts as low as possible.¹³ The total amount of funding from the generic industry will be drawn from a broad funding source, including an estimated 2,000 FDF and API manufacturers supporting ANDAs, prior approval supplements (PASs), and drug master files (DMFs) as well as application fees which cover ANDAs, PASs and DMFs.

¹² GDUFA includes an expedited review of first to file Paragraph IV ANDAs during the first two years of the program (before reportable review metrics apply starting in year 3) in an effort to minimize inadvertent forfeiture risk for failure to obtain a tentative approval within 30 months of submission.

¹³ "An Economic Analysis of Generic Drug Usage in the U.S." Independent Analysis by IMS Health, Sept. 2011.

The fee package is structured so that 80 percent of the total will be derived from the FDF industry and 20 percent from the API industry. The variety of funding sources for the program will assure that participants in the generic drug industry, whether FDF or API manufacturers, appropriately share the financial expense and benefits of the program. Of the majority of the total generic drug user fee package, 70 percent will be derived from facility fees, while the remaining 30 percent shall be derived from application fees. Both FDF and API manufacturing facilities listed or referenced in a pending or approved ANDA will pay a facility fee. Foreign facilities will include a modest fee differential to reflect the average additional costs of foreign inspections based on data determined by the agency.¹⁴ The remaining 30 percent of the total generic drug user fee package will be derived from application fees. Application fees include an ANDA, PAS, and DMF application fee. In addition, in the first year of the program there will be a one time backlog fee for ANDAs that are pending on October 1, 2012, and have not received tentative approval.

In return for the fees, the industry and FDA have agreed upon a number of additional goals, metrics, and efficiencies set forth in detail in a negotiated goals letter. Importantly, with these resources, FDA has committed to, among other metrics: (1) review and act on 90 percent of new ANDAs within 10 months from submission; (2) act on 90 percent of all ANDAs and PASs that are pending in the backlog (an estimated 2,700 applications); and (3) achieve parity of GMP

¹⁴ According to FDA's *Pathway to Global Product Safety and Quality* Special Report, Exhibit 10, published in 2011, the average cost of foreign inspections (\$52,000) is two times the average cost of a domestic inspection (\$23,000).

inspections for foreign and domestic facilities by the fifth year of the user fee program.

Notably, given that many facilities make both brand and generic products, it is expected that the generic drug program will pay for biennial, risk-based GMP inspections of FDF and API facilities representing more than 78% of the total U.S. pharmaceutical market, including both brand and generic products.

Mylan is proud of all that GDUFA will accomplish, and the historic paradigm shift that it establishes. The generic industry, which accounts for 78 percent of all prescription dispensed in the U.S. has stepped up to the plate to help provide FDA with resources to address the industry-wide, both branded and generic challenges caused by the global drug supply and the corresponding increase in FDA's workload. However, for it to truly be successful, and to achieve the lasting change that I believe we all wish to see, the currently outdated U.S. law must also be amended to reflect the 21st century needs of the FDA in regulating the nation's global drug supply.

B. FDA's governing law on drug oversight is reflective of the 1938 Pharmaceutical Industry, not today's climate

Every consumer should have the peace of mind in knowing that every prescription, brand or generic, dispensed in the United States, is held to the same standard of quality regardless of whether the product or its ingredients originated in the U.S. or outside its borders. Unfortunately, the current provisions of U.S. law, based largely on FDCA, were passed in 1938 when the source of our drug supply looked quite different than today.

One of the key ways FDA carries out its oversight responsibilities of ensuring continued compliance with the quality standards required of all prescription drugs sold in the U.S. (branded and generic) is by conducting on-site facility inspections. Unlike pre-approval inspections which occur prior to a specific product approval, routine surveillance inspections (known as GMP inspections) ensure that facilities are continuing to meet their obligation of producing safe products after approval in accordance with rigorous good manufacturing practices and are intended to identify potential concerns or observations before an issue emerges that may later interrupt or impact the safety or efficacy of the drug supply. The FDCA requires American manufacturers associated with pharmaceutical production to undergo a routine GMP inspection every two years to ensure that these facilities are complying with rigorous GMP standards.¹⁵ However, the FDCA does not impose the same biennial inspection requirement on foreign facilities. The average GMP facility inspection of foreign facilities occurs every nine years compared to every two years for a U.S.-based facility.¹⁶ According to a 2010 GAO report, the FDA inspected just 11 percent of the 3,765 foreign establishments in its database in 2009. GAO estimates that some foreign facilities supplying the U.S. market may have never undergone a GMP inspection.¹⁷

C. Unlevel Playing Field that Threatens American Competitiveness

¹⁵ See 21 U.S.C. § 360.

¹⁶ U.S. Government Accountability Office. Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed (Publication No. GAO-10-961). (September 2010).

¹⁷ *Id.*

The significant disparity in the degree of FDA oversight experienced by domestic facilities compared to foreign facilities creates an unlevel playing field, reducing the ability of American businesses, which have built in costs for regular GMP compliance, to compete. The U.S. already has the second-highest combined federal-state corporate tax rate, 39.2 percent, and according to a recent report by Pew Health Group, complying with quality systems and FDA regulations represents approximately 25 percent of a drug manufacturers' operating costs.¹⁸ U.S.-based facilities participating in both the U.S. and global pharmaceutical market should not be competitively disadvantaged and effectively encouraged to move jobs to outside of the U.S. as a result of an antiquated law that is impeding FDA from carrying out its oversight responsibilities over all players supplying the U.S. pharmaceutical market.

Mandating FDA risk-based biennial GMP inspections of all facilities, foreign and domestic, will improve quality and create a level playing field for all pharmaceutical manufacturers. Inspection parity will also benefit foreign facilities, as well as small and first time entrants to the industry, which are currently disadvantaged by delays in gaining approval for new products due to a lack of a recent inspection history, which is required before a new product can be approved.

Congress recently updated the FDCA to help equip the FDA to carry out its mission of ensuring food safety in an increasingly globalized food supply.¹⁹ With respect to the global drug supply, however, FDA still effectively operates

¹⁸ Pew Health Group, *After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs*, at 27.

¹⁹ FDA Food Safety Modernization Act, Public Law 111-353.

within the constraints of the FDCA of 1938, the scope and provisions of which are largely domestic. The agency recently acknowledged that when it comes to drug oversight, FDA is “looking to Congress to modernize its antiquated authorities so that FDA’s legal tools keep pace with globalization.”²⁰ Without changes to laws governing the U.S. drug supply necessary to fully fund FDA’s oversight of today’s complex and global drug supply, the significant challenges to the U.S. pharmaceutical marketplace will continue and likely increase.

Ensuring that all contributors to the U.S. drug system, both foreign and domestic, are held to the same quality standard is a critical issue for the entire pharmaceutical industry – brand and generic alike. Amending the FDCA of 1938, and in particular, mandating risk-based routine FDA GMP inspections of all domestic and foreign pharmaceutical facilities every two years, will improve the quality, consistency and availability of finished product and active ingredients within the drug supply chain.

Additionally, the lack of routine surveillance GMP inspections of foreign facilities has allowed weak links to enter the supply chain, resulting in potential market disruptions or other adverse events. GMP inspections are intended to, among other things, detect and address such quality concerns early in the manufacturing process.

The backlog in routine foreign GMP surveillance inspections also causes notable delays in introducing new prescription drugs to consumers, including delays in approving products that serve unmet medical needs and offer more affordable options such as generic drugs. As I described previously, approval of

²⁰ FDA, Special Report, Pathway to Global Product Safety and Quality, pg 4. (July 2011)

a drug requires a recent inspection history of the relevant manufacturing facility. Many of the facilities producing new drugs are based abroad and are therefore waiting years to be inspected.

Globalizing FDA by enhancing the law authorizing FDA to oversee today's complex and global drug supply to reflect the significant challenges to the U.S. pharmaceutical marketplace, will allow FDA to respond to the increasing challenges it faces in regulating the nation's drug supply. We urge Congress to move forward in updating the 1938 law and adopting the Generic Drug User Fee Program as negotiated with the FDA and industry.

V. DRUG SHORTAGES

As noted above, an important benefit of the generic drug user fee program is to identify and address potential weak links in the supply chain as early as possible. By conducting routine, on-site surveillance inspections (GMP inspections) of facilities located in the U.S. and abroad to ensure that they comply with rigorous GMP standards, FDA will be positioned to detect market disruptions before they occur. GMP inspections are critical to the Agency's ability to identify potential concerns before an issue emerges that may later interrupt or impact the safety or efficacy of the supply chain. We believe drug shortages could be reduced as FDA achieves parity in GMP inspections of foreign and domestic facilities using a risk based approach. Additionally, the additional resources under GDUFA will decrease review times and ensure more timely access to new generic products, including those that address an unmet medical need or those in short supply. Strengthening the supply chain – a key

aim of GDUFA through routine, GMP inspections as well as transparency initiatives that require the identification and registration of facilities involved in the supply chain – will provide a more holistic solution. To make lasting change, we urge Congress to make the necessary updates to the FDCA of 1938 to give FDA the authority it needs to carry out its mission in today's global drug supply.

VI. BIOSIMILARS USER FEE

The Affordable Care Act of 2010 directed FDA to develop a user fee program for review of biosimilar and interchangeable biological products in an effort to expedite access to biogenerics. Unlike GDUFA, the Biosimilars User Fee Act proposal before you was based on the Biologics Price Competition and Innovation Act (BPCIA), which was passed into law in March 2010 as part of the Patient Protection and Affordable Care Act (PPACA). Therefore, the opportunity to take a holistic approach to this user fee proposal, as the generic industry was able to do with GDUFA, was not available. While user fees were mandated and shaped by the Affordable Care Act in order to help expedite access to more affordable biogenerics, achieving the true savings Americans deserve through more affordable biogenerics will require much additional work and resources from Congress. It is telling that nearly two years have passed since the biogenerics approval pathway was enacted into law, and to date, no biogeneric has been approved by FDA nor has FDA released any meaningful guidance to promote a workable pathway to deliver access to safe and effective biogenerics. This was clearly not the result Congress intended when it was estimated that the biogenerics pathway would save American taxpayers and the federal

government billions of dollars over the 10 years following its passage in 2010.²¹ Mylan looks forward to working with Congress, GPhA and other stakeholders in ensuring a workable pathway to make available safe, effective and affordable biogenerics.

VII. CONCLUSION

In conclusion, Mr. Chairman, Mylan urges Congress to pass the Generic Drug User Fee Program as unanimously ratified by industry and update the Federal Food Drug and Cosmetic of 1938. Only by taking these steps can we further reduce government and taxpayer healthcare spending through more timely access to affordable generic medicine; ensure American competitiveness by addressing the unlevel playing field currently faced by U.S. manufacturers through inspection rates that are four times that of foreign competitors; and equip FDA with the authority it needs to carry out its mission of protecting the drug supply chain in today's highly globalized industry.

Thank you. I would be happy to address any questions of the committee.

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²¹ See, e.g., CBO, H.R. 4872, Reconciliation Act Of 2010 (Final Health Care Legislation), Cost Estimate For The Amendment In The Nature Of A Substitute For H.R. 4872, Incorporating A Proposed Manager's Amendment Made Public On March 20, 2010, available at <http://www.cbo.gov/ftpdocs/113xx/doc11379/AmendReconProp.pdf>

Mr. PITTS. Thank you. Mr. Gaugh, you are recognized for 5 minutes to summarize your opening statement.

STATEMENT OF DAVID GAUGH

Mr. GAUGH. Thank you. Good morning, Chairman Pitts, Ranking Member Pallone, and members of the subcommittee. Thank you for inviting me to testify on these very timely and important issues. I am David Gaugh, Vice President for Regulatory Sciences at the Generic Pharmaceutical Association and a licensed pharmacist. GPhA represents the manufacturers and distributors of finished-dose generic pharmaceuticals, bulk pharmaceutical chemicals, and suppliers to the generic industry. Generic pharmaceuticals fill 78 percent of all prescriptions dispensed in the United States but consume just 25 percent of the spending for prescription medicines.

I would like to begin by commending the committee for your continued focus on these most important issues that you are examining today. Though I have just begun my time with GPhA, I have been working in and around the generic industry for more than 2 decades and have witnessed firsthand the industry's remarkable growth and the vital role it plays in the lives of Americans every day. This growth of the generic industry has also served to underscore the critical importance and the role of the Food and Drug Administration. As shown by these two historic user fee agreements and our continued efforts to address drug shortages, the level of cooperation between the industry and the FDA has never been greater. It is our hope this collaboration will continue and even extend throughout the interactions for future activities with the Agencies.

However, the Agency remains underfunded and the responsibilities of ensuring safe and effective access for affordable medications is shared with the entire pharmaceutical industry, not just with the FDA. This is why the generic industry has stepped up to the plate, and I would be pleased to provide some examples.

Currently, well more than 2,000 generic drug applications are awaiting approval for the FDA Office of Generic Drugs and average approval time for these applications is now stretched to 32 months. Unfortunately, the backlog keeps growing for these generic drugs, keeps off market competitors, and prevents the prices from continuing to go down further. The proposed Generic Drug User Fee, or GDUFA, that we are discussing today will provide the FDA with nearly \$1.5 billion over the next 5 years to help alleviate this backlog and expedite consumers to new generic drugs. It will also take the historic step of holding all players contributing to the U.S. generic drug system, both foreign and domestic, to the same inspection standards and enhance FDA's ability to identify and require the registration of active pharmaceutical ingredients and finish dosage from manufacturers involved in the production of the products being sold in the U.S.

It is paramount that as we work and save the future of our country's generic industry, we also work with the FDA to bring them into the 21st Century and ensure that the Agency's authority to achieve its mission and the goals are kept up to date. This is exemplified by the user fee program we are discussing today, both GDUFA and the biosimilar fee structure.

During the biosimilar fee negotiations, GPhA expressed its support for user fee funding to provide FDA with adequate resources to apply consistent regulatory standards to all biologics. Both industry and patients will benefit from this user fee program by gaining a higher degree of certainty in the timeliness of the applications, the review, and their approval. It is important to emphasize that the funding provided by these user fee programs is in addition to and not a substitute for congressional appropriations.

And while the programs provide an excellent framework for the industry to help support the growing global needs of the FDA, they do not completely solve the problems. For example, some manufacturers are using the REMS program as a way to delay generic competition. For products that require a full REMS and distribution in accordance with restricted systems, REMS manufacturers are making it difficult for the generic manufacturers to acquire samples of products so that they can actually run the tests on the products to be able to produce the exact bioequivalent product in a generic form. GPhA also supports the adoption of a Federal drug tracking system with uniformed standards across all States to prevent a patchwork by state law.

Now, let me address the drug shortage crisis. The generic pharmaceutical industry has spearheaded the development of an unprecedented multi-stakeholder collaboration, which we believe will accelerate the recovery of certain critical drugs in short supply that are in patient need. This private sector solution, which we have labeled as the Accelerated Recovery Initiative, is designed to provide a more accurate, timely, and comprehensive view of the critical drugs and drug shortage, provide greater visibility to potential shortages of those critical drugs that are established for potential loss, and voluntary production adjustments to lessen and even eliminate certain current drug shortages. This initiative is predicated on voluntary communication between an independent third party and all key stakeholders involved in the approval, the manufacturing, and the distribution of drugs that are in shortage.

In conclusion, Mr. Chairman, it is our hope that Congress will act on these historic user fee proposals as an expeditious process. Nothing is more important to our industry than ensuring patients have access to life saving generic medications they require, and with a joint effort among all involved, we believe we can continue to make significant steps towards accomplishing this goal.

Thank you, and I look forward to your questions.

[The prepared statement of Mr. Gaugh follows:]

SUMMARY OF THE GENERIC PHARMACEUTICAL ASSOCIATION TESTIMONY
BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH
UNITED STATES HOUSE OF REPRESENTATIVES - FEBRUARY 9, 2012
“REVIEW OF THE PROPOSED GENERIC DRUG AND BIOSIMILARS USER FEES AND FURTHER
EXAMINATION OF DRUG SHORTAGES”

I am David Gaugh, Vice President for Regulatory Sciences at the Generic Pharmaceutical Association and a licensed pharmacist. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals and suppliers of other goods and services to the generic industry. Generic pharmaceuticals fill 78 percent of the prescriptions dispensed in the U.S. but consume just 25 percent of the total drug spending.

Landmark User Fee Programs Will Provide Additional Resources

Currently, more than 2,000 generic drug applications are awaiting approval from the FDA’s Office of Generic Drugs (OGD), and the average approval time for an application is now stretching beyond 30 months. The Generic Drug User Fee Act (GDUFA) will help alleviate the backlog and expedite consumer access to generic drugs, while also enhancing drug quality and safety. FDA will receive \$299 million per year over the five-year GDUFA program, or about \$1.5 billion in total. The new user fee program will also establish performance goals for the FDA. The agreement’s performance goals call for FDA to complete, by the end of year five, the review of 90 percent of all ANDAs that are pending on October 1, 2012 — effectively eliminating the current application backlog. By the end of the program’s fifth year, GDUFA calls on the FDA to review 90 percent of ANDAs within 10 months after they are submitted — almost two years faster than today’s average review time. GDUFA also takes the unprecedented step of holding all players contributing to the U.S. generic drug system, foreign or domestic, to the same inspection standards, and enhances FDA’s ability to identify and require the registration of API and finished dosage form manufacturers involved in each generic drug product sold in the U.S.

The Biosimilars User Fee Act will benefit both patients and industry by providing a higher degree of certainty in the timeliness of application reviews. The program creates a separate review platform for biosimilar sponsors that will be jointly financed annually by industry and the FDA through \$20 million in Congressional appropriations and then supplemented by user fees equivalent to those under the Prescription Drug User Fee Act. The program’s performance goals call for FDA, by the end of the program’s fifth year, to review 90 percent of the original biosimilar applications it receives within 10 months of their submission.

Addressing the Drug Shortage Crisis

GPhA is committed to working with the FDA and all stakeholders to minimize current drug shortages and prevent future shortages from occurring. Causal factors of drug shortages are numerous and do not apply in every case. They include everything from an insufficient supply of available raw materials, to increasing consumer demand, to decreasing available capacity, to inadequate and delayed communications about shortages — all within the supply chain and also within and among the FDA’s enforcement and drug shortages personnel. The manufacturing community has been extremely visible in working with all stakeholders, especially the FDA, to find suitable solutions that accelerate the availability of critical drugs in short supply. A group of generic manufacturers, including both GPhA and non-GPhA members, that represent approximately 80 percent of the generic sterile injectable products sold in the U.S. today, are proposing the **Accelerated Recovery Initiative (ARI)**, which is a private sector solution that is predicated on voluntary communication between stakeholders in the manufacture and distribution of generic injectable drugs in shortage.

Supply Chain Security

GPhA strongly supports the unprecedented steps taken in GDUFA to ensure that all contributors to the U.S. drug system, both foreign and domestic, are held to the same quality standard. GPhA further supports a “risk-based” model for inspections that prioritizes inspections according to a company’s safety and compliance track record. GPhA recommends that Congress adopt a federal drug tracking system with uniform standards across all states. As a member of the Pharmaceutical Distribution Security Alliance (PDSA), GPhA, in consensus with other supply chain partners, supports the RxTEC model, which will increase patient safety and help to achieve the goals we share with the FDA.



TESTIMONY OF DAVID GAUGH, R.PH.

VICE PRESIDENT FOR REGULATORY SCIENCES

GENERIC PHARMACEUTICAL ASSOCIATION

**REVIEW OF THE PROPOSED GENERIC DRUG AND BIOSIMILARS
USER FEES AND FURTHER EXAMINATION OF DRUG
SHORTAGES**

BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

FEBRUARY 9, 2012

Good morning Chairmen Pitts and Upton, Ranking Members Pallone and Waxman and Members of the House Energy and Commerce Subcommittee on Health. Thank you for inviting me to testify before your subcommittee on these very timely and important subjects.

I am David Gaugh, Vice President for Regulatory Sciences at the Generic Pharmaceutical Association and a licensed pharmacist. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals and suppliers of other goods and services to the generic industry. Generic pharmaceuticals now fill 78 percent of all prescriptions dispensed in the U.S., but consume just 25 percent of the total drug spending for prescription medicines.

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

Prior to joining GPhA, I was Vice President and General Manager for Bedford Laboratories, the generic injectable division of Ben Venue Laboratories, I have also served as Senior Director, Pharmacy Contracting and Marketing, for VHA/Novation, one

of the largest Group Purchasing Organizations in the U.S., and was System Director of Pharmacy for a regional referral tertiary-care healthcare system in the Midwest.

Introduction

I would like to begin today by commending the Committee for your continued focus on the important issues we will examine today. Though I am just beginning my time at GPhA, I have worked in and around the generic industry for more than two decades and have witnessed firsthand the industry's remarkable growth and the vital role it plays in the lives of Americans every day. By providing consumers access to safe and effective medicines at an affordable price, the generic industry fills an essential role not only for patients, but for our health care system and, indeed, our national economy.

This growth in the generic industry has also served to underscore the critically important role of the Food and Drug Administration (FDA). As I will highlight, the level of cooperation between industry and the FDA has never been greater. The two historic user fee agreements and continual efforts to address drug shortages we are discussing today, represents only a small measure of our ongoing collaboration.

As evidenced by these accomplishments, the FDA's work during this period of growth for the generic industry has been extraordinary. Thanks to their efforts, the U.S. drug supply remains the safest of anywhere in the world, and the FDA's drug approval and inspection processes represent the gold standard for regulatory agencies worldwide.

However, the agency remains underfunded, and the responsibility of ensuring safety and access to affordable medicines is a shared one that rests with the entire pharmaceutical industry, not just the FDA. That is why the generic industry has stepped up to the plate to help provide the FDA with resources to address the ongoing challenges caused by an increasingly global drug supply, the increase in the agency's workload and the regulation of new and complex technologies.

Throughout much of the last 12 months, GPhA and our member companies worked closely with the FDA to negotiate two separate user fee programs designed to help the agency obtain additional resources in this global age and to ensure all participants in the U.S. generic drug system, whether U.S.-based or foreign, comply with all of our country's strict quality standards. Most importantly, the programs will make certain that all Americans receive timely access to safe, effective and affordable generic drugs. Let me provide some more details.

Landmark User Fee Programs Will Provide Additional Resources

Currently, more than 2,000 generic drug applications are awaiting approval from the FDA's Office of Generic Drugs (OGD), and the average approval time for an application is now stretching beyond 30 months, five times longer than the statutory six-month review time called for by Hatch-Waxman. Unfortunately, this backlog keeps safe, low-

cost generic drugs off the market and reduces competition that may drive down drug prices further.

The proposed Generic Drug User Fee Act, or GDUFA, that we are discussing today will help alleviate the backlog and expedite consumer access to generic drugs, while also enhancing drug quality and safety by ensuring inspection parity among both foreign and domestic manufacturing sites.

Specifically, FDA will receive \$299 million per year over the five-year GDUFA program, or about \$1.5 billion in total. Of that funding, 80 percent, or about \$240 million, will come from finished-dose manufacturers, and the remaining 20 percent will be paid by manufacturers of active pharmaceutical ingredients. Thirty percent of the funding will stem from application fees and 70 percent will be derived from fees on manufacturing sites, or facility fees.

Splitting the fees in this manner will provide the FDA with a predictable source of annual income, as the number of facilities manufacturing generic drugs on a yearly basis provides a more consistent figure than the number of generic drug applications submitted. Finished dose facilities that manufacture both generic and brand medications will be required to pay both a Prescription Drug User Fee Act facility fee and a GDUFA facility fee.

The new user fee program will also establish performance goals for the FDA. As part of these goals, GDUFA calls for the agency to complete, by the end of year five, the review of 90 percent of all generic drug applications — commonly referred to as Abbreviated New Drug Applications, or ANDAs — that are pending on October 1, 2012 — the proposed start date for the program. By achieving this goal, the GDUFA agreement will effectively eliminate the current application backlog.

In addition, also by the end of the program's fifth year, GDUFA calls on the FDA to review 90 percent of ANDAs within 10 months after they are submitted — almost two years faster than today's average review time.

These are great strides that will go a long way toward ensuring patients have timely access to safe and effective generic medicines for years to come. But GPhA also recognizes that while providing earlier access to effective medicines is critical — and the key aim of all other existing user fee programs — an equally important pillar of FDA's and industry's mission is ensuring drug safety.

Since the enactment of the Federal Food, Drug and Cosmetic Act in 1938, the core public health mission of the FDA has been to protect and promote the public's health. As part of that mission, the FDA has a critical responsibility to ensure the safety, efficacy and security of the entire U.S. drug supply, both brand and generic. Ensuring a safe and effective drug supply, however, is significantly more challenging today than it

was in 1938 due to the increasing globalization of drug manufacturing, supply and testing and an increase in FDA-regulated drug products.

GPhA has long-maintained that, in light of this increasing globalization and with nearly 40 percent of all the prescription drugs in the U.S. being imported, the FDA needs more resources to ensure adequate oversight of the nation's drug supply.

A 2010 Government Accountability Office (GAO) report found that FDA was able to conduct Good Manufacturing Practice, or GMP, inspections at only 11 percent of the foreign establishments in its database, compared to 40 percent of the domestic sites it inspected. According to the GAO, in the absence of a paradigm shift, it would take FDA nine years to inspect all foreign facilities.

That is why GDUFA takes the unprecedented step of holding all players contributing to the U.S. generic drug system, foreign or domestic, to the same inspection standards, and enhances FDA's ability to identify and require the registration of active pharmaceutical ingredient and finished dosage form manufacturers involved in each generic drug product sold in the U.S. The program will significantly improve the resources the FDA has to do this important work, ensuring that it can be done with increasing speed, but without any sacrifice to today's high quality standards.

It is important to emphasize that the funding provided by GDUFA is in addition to, not a substitute for, Congressional appropriations. And while the program provides an

excellent framework for industry to help support the growing global needs of FDA, it does not completely solve the problem. It is paramount that, as we work to shape the future of our country's generic drug industry, we also work to bring the FDA into the 21st century and ensure that the agency's authorities to achieve its mission in this global age are up to date.

In many ways, this process is already underway. Perhaps the best and most immediate example rests with the other user fee program we will discuss today — for generic biologic drugs, or biosimilars.

Biologic medicines are often the only lifesaving treatments for many of the most severe diseases encountered by patients today. In many respects, they represent the future of medicine. Their high price tag, however, can keep them out of reach for many patients. The cost of biologics is increasing annually at a faster pace than almost any other component in health care. As proven with chemical prescription drugs, competition from generic biologic drugs will be the most important factor in holding down the future costs of these lifesaving medicines.

With the FDA still working to determine the process by which these products will be approved, GPhA continues to stress the importance of creating a workable regulatory mechanism that does not serve as a barrier to competition, but rather ensures the robust competition needed to lower costs and spur future innovation. If such a system is not put in place, it is our fear that the exponential growth of biologics over the next 10

to 20 years, without adequate generic alternatives, could bankrupt our health care system and the national economy. Moreover, the lack of lower-cost generic biologics will keep vital treatments away from the patients who need them most.

Within our organization, we represent manufacturers who currently produce high-quality, safe and effective biosimilars approved in Europe and other regulated markets around the world. These member companies are dedicated to bringing the same level of access and affordability for these critical medicines to U.S. patients.

During the biosimilar user fee negotiations, GPhA expressed its support for user fee funding to provide FDA with adequate resources to apply consistent regulatory standards to all biologics, and review new applications as they are filed. Both industry and patients will benefit from this user fee program by gaining a higher degree of certainty in the timeliness of application reviews.

The proposed program creates a separate review platform for biosimilar sponsors, to be financed annually through \$20 million of the funds appropriated to the FDA and supplemented by user fees equivalent to those under the Prescription Drug User Fee Act, albeit with a portion of the application fee paid during the biosimilar development phase to support earlier resourcing for product reviews. Similar to GDUFA, the program also includes performance goals for the FDA, which call for the agency, by the end of the program's fifth year, to review 90 percent of the original biosimilar applications it receives within 10 months of their submission.

We applaud the FDA for recognizing the importance of biosimilars, and the need to apply state-of-the-art science in all agency activities governing the review and approval of these important drugs.

Through both of these user fee agreements, the generic industry has truly stepped up to the plate to do our part to help insure U.S. drug safety, establish a more level playing field among all participants in the U.S. pharmaceutical supply chain and significantly reduce the time needed to commercialize a generic drug.

By designing the programs to spread fees across multiple stakeholders and sources to keep individual amounts as low as possible, the programs will help assure that American consumers continue to receive the significant cost savings from generics that, over the past dozen years, have provided more than \$1 trillion in savings to the nation's health care system.

Addressing the Drug Shortage Crisis

GPhA believes strongly that the collaboration between industry, the FDA and other stakeholders shown during the development of the user fee programs should serve as a model for other areas, in particular as we work to eliminate existing shortages of critical drugs and minimize the potential for future shortages.

As members of the public who also are affected by shortages, the generic pharmaceutical industry is acutely aware of the distress caused to patients, families and clinicians by the shortage of critical drugs. Drug shortages represent a complex, multi-faceted issue and our industry has, and will continue, to work tirelessly to be part of the solution.

Before examining how best to respond to drug shortages it is important to understand why they are occurring. Contrary to some media reports, drug shortages are typically not caused by a manufacturer's decision to voluntarily discontinue supplying the product, and manufacturers do not — and would never — deliberately reduce the supply of essential medicines to push prices up. There can be no question that generic manufacturers are in the business of supplying quality medicines and assuring that consumers and patients have access to the drugs they need.

Causal factors of drug shortages, rather, are numerous and do not apply in every case. They include everything from an insufficient supply of available raw materials, to increasing consumer demand, to decreasing available capacity, to inadequate and delayed communications about shortages — all within the supply chain and also within and among the FDA's enforcement and drug shortages personnel.

GPhA also acknowledges that while factors contributing to drug shortages are many and complex, roughly half of the reported shortages have been attributed to difficulties associated with the manufacturing and release of generic sterile injectable products.

The manufacturing community has been responsive to this issue and has been extremely active in working with all stakeholders, and especially the FDA, to find suitable solutions that accelerate the availability of critical drugs in short supply.

Collaboration Among Stakeholders is Needed

GPhA also believes it is critical that generic manufacturers, and all stakeholders, continue to work together in an effort to solve the problem. As an industry whose entire business model is to make quality medicines available and affordable to all, we are acutely aware that a lack of supply of a critical drug can be devastating, even if it impacts only one patient.

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

Accelerated Recovery Initiative (ARI)

The goal of ARI is to put in place industry practices that provide a more accurate, timely and comprehensive view of the current drug shortage situation, provide greater visibility to potential shortages solutions and establish practices that allow for potential, voluntary production adjustments to lessen or eliminate the impact of a current shortage. Given that over 200 products are currently identified by the FDA Drug Shortage staff, the initial scope of the initiative will focus only on those products deemed most critical, sterile generic injectable products. We will continue to fine tune the inclusion criteria with a focus on products that have few manufacturing options and no therapeutic alternative.

As I noted, this initiative is predicated on voluntary communication between an independent third party and stakeholders involved in the manufacturing and distribution of generic injectable drugs in shortage. In addition, this multi-stakeholder approach will provide additional information focusing on real time decisions and actions proposed by regulatory agencies and their potential impact on critical supply.

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

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

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

Under the ARI, the impartial third party will gather and disseminate the supply information in compliance with all current market regulations and under terms of strict confidentiality. This independent third party will be supplied with data from manufacturers related to drugs currently in shortage or expected to go into shortage, including the name of the drug, the expected duration of the shortage and internal reviews of a product's production and release data to identify production capabilities that will allow us to respond to any market shortage. Wholesalers and distributors will also supply current product availability data to assure a complete review of all available inventories in their pipelines.

The independent third party will then aggregate the data to provide an overall view of the projected available supply by product, as defined by critical product criteria, compared to the total market need. If the data reveals gaps in market supply that require FDA intervention, the information will be provided by the independent third party to the FDA Drug Shortage staff so that they may help to develop solutions with the manufacturers.

In addition, GPO's also have an important role to play. Their focus will be to assure that timely and accurate information is readily available between all affiliated members, institutions and customers, and the independent third party.

The last step of ARI focuses on FDA. The agency deserves tremendous credit for the work it is currently doing to expedite regulatory reviews and work closely with manufacturers. However, there is still more that must be done, and manufacturers would be aided by a formal process specifically designed to facilitate communications related to drug shortage regulatory issues.

The formation of a FDA drug shortage management team could more effectively address current drug shortages and minimize future shortage events. The industry strongly encourages the establishment of this high-level FDA drug shortage management team, which would include representation from key agency offices; the FDA's Center for Drug Evaluation and Research medical staff, Office of Compliance, Drug Shortage staff and Office of Regulatory Affairs.

This team would provide an avenue for timely access to FDA decision makers by the pharmaceutical industry to review strategies for addressing or averting drug shortages. This high-level FDA team could provide the expertise and the appropriate level of authority to effectuate rapid decisions on steps to address drug shortages by being empowered to evaluate issues such as expediting reviews of pending supplements, which enable industry to address shortages of critical drug products.

Our industry is currently working with FDA and other stakeholders to implement the ARI in parallel with our other recommendations in order to increase the channels of communication and strengthen our collective ability to supply patients with the medicines they critically need.

Supply Chain Security

Finally, as we work to resolve these shortages of critical drugs and prevent future shortages from occurring, I would also like to mention briefly the vital importance of securing the supply chain that patients rely on to provide them with these medications.

GPhA and our member companies are committed to doing everything possible to work with Congress and the FDA to ensure that adequate oversight of the nation's drug supply is in place to ensure its safety. The generic pharmaceutical industry is among the most highly regulated in the world, with strict rules governing the development,

manufacture, approval, packaging, marketing and post-marketing surveillance of prescription drugs by the FDA.

As noted previously, GPhA strongly supports the unprecedented steps taken in GDUFA to ensure that all contributors to the U.S. drug system, both foreign and domestic, are held to the same quality standard.

GPhA further supports a “risk-based” model for inspections that prioritizes inspections according to a company’s safety and compliance track record. This system would ensure that questionable or problematic facilities receive a comprehensive review and evaluation sooner, rather than later, or not at all as can be the case under the current system. Facilities with strong records of compliance and positive inspections would be placed further down on the inspection schedule, allowing the agency to prioritize its immediate attention on facilities that have never had an inspection or that have a history of compliance issues.

GPhA recommends that Congress adopt a federal drug tracking system with uniform standards across all states. Given that products are distributed throughout interstate commerce and across state lines, having multiple standards will be problematic. The challenge to implementation will be to ensure that the technology is reliable and feasible in light of numerous economic, technical and logistical factors, so that the end product delivers patient safety and does not result in increased costs to consumers and payers.

As a member of the Pharmaceutical Distribution Security Alliance (PDSA), a multi-stakeholder group working to develop a national model for drug tracking, GPhA, in consensus with other supply chain partners, supports the RxTEC model, which will increase patient safety and help to achieve the goals we share with the FDA.

We believe this model will help prevent the introduction of counterfeit drugs, facilitate their identification, provide accountability for the movement of drugs by supply chain participants and improve the efficiency and effectiveness of recalls. Establishing a national uniform drug tracking system, as opposed to a system based on a patchwork of state laws and regulations, is critical to achieving these goals.

Conclusion

In conclusion, Mr. Chairman, this truly is a historic time for GPhA. The two user fee proposals now before the Committee will shape the future of our industry for years to come. And the unprecedented level of collaboration between industry, the FDA and other stakeholders that it took to reach these agreements will continue to serve us well as we work to minimize current drug shortages and prevent future shortages from occurring. Nothing is more important to our industry than ensuring patients have access to the lifesaving generic medications they require, and with a joint effort among all involved, we believe we can continue to make significant steps toward accomplishing this goal. Thank you.

Mr. PITTS. The Chair thanks the gentleman and now recognizes Dr. Greene for 5 minutes to summarize your opening statement.

STATEMENT OF BILL GREENE

Mr. GREENE. Chairman Pitts and other members of the committee, I am grateful for the opportunity to address you today as a representative of St. Jude's Children's Research Hospital and also a representative of colleagues at children's hospitals throughout the United States. As you know, I am chief pharmaceutical officer at St. Jude and at St. Jude we are committed to developing research that leads to new cures for children with catastrophic diseases. We are also committed to providing unsurpassed clinical care for those patients. I am really grateful that you would offer me time to share some comments.

My short testimony—if we can have some slides here—I would like to share three ways Congress can help alleviate drug shortages for the pediatric community. But first, I would like to begin by putting a face to my discussion, and it doesn't look like the face will be able to be displayed.

I can tell the story of Lucy, who is a 5-year-old from Covington, Tennessee. Lucy and her family have given me permission to share her story as a way of illustrating the challenges that drug shortages pose for patient care and for the caregivers that are providing that care. She is being treated for medulla blastoma, which is a type of brain cancer. She has been doing well, and last spring she was being treated in her prescribed course of treatment and was being supported by intravenous nutritional support. She began to develop symptoms, rapid eye movements, blurred vision, other visual changes, some gait changes that caused her care team to suspect that her cancer was relapsing. So she was admitted to the hospital and worked up. Fortunately, during that time, she was treated with intravenous thiamin. She experienced a dramatic recovery and was able to continue with her treatment course.

The interesting background on this issue is that the cause of the thiamin deficiency was very simple. We were simply unable to secure intravenous preparations of multivitamins to add to her intravenous nutritional support. That caused the thiamin deficiency, the thiamin deficiency caused the symptoms, the symptoms resulted in a hospital admission. This was a preventable admission and it should not have happened.

You are aware that the number of drug shortages occurring in the United States has increased dramatically in recent years. While not all of these shortages have directly affected St. Jude, the number of shortages affecting us have increased dramatically. If I were able to show my second slide, I would be able to illustrate to you that we have experienced a 10-fold increase in the number of shortages requiring action at our organization since 2008. In the last 2 months alone, January and December, I have had to issue communications to our clinical staff on 14 separate occasions. Now, once that requires my action, those are important drug shortages that impact patient care—14 times in the last 2 months.

Our drug shortages threaten our Nation's healthcare system and especially children in three distinct ways. First, we know that we cannot always provide the best care for these patients. Second, we

know that shortages do affect research that cause modifications for protocols, sometimes delays in research and terminations. We know that at least 85 children's oncology group protocols that have been affected by shortages. And third, we know that all of these shortages definitely add real cost to the system. I know the subcommittee has previously heard testimony of this type. Much data has been shared. Many of the comments today have been very interesting and helpful. It is now time for immediate action.

I have three points I would like to make about what Congress can do to help. First, I urge Congress immediately to pass legislation to give the Food and Drug Administration the tools that it needs to prevent and minimize the impact these shortages have on pediatric care and research. The FDA has been effective in minimizing the impact of shortages when appropriate communication is made to the Agency. Their efforts have avoided almost 200 shortages in 2011. Congress can strengthen their reporting system by enacting H.R. 2245, Senate Bill 296, to give the FDA more complete knowledge of permanent and temporary supply chain disruptions in advance and allowing the FDA to facilitate its communications with caregivers like me.

Second, I urge Congress to give the FDA the resources and authority it needs to combat drug shortages in a proactive manner. While the FDA's efforts have been laudable, these efforts have been largely reactive. Once a shortage has evolved, we know patients are going to be affected. The Agency must have what it needs to develop proactive approaches to predict and prevent shortages and the FDA should have sophisticated systems in place facilitating forecasting, prediction, and enabling proactive work with suppliers and purchasers to prevent shortages from ever occurring. Further, other relevant agencies such as the DEA must work closely, collaboratively, with the FDA to combat these shortages.

Third, Congress must ensure that in any solution it develops, pediatric protections are built in and pediatric experts are broadly engaged. Children require medications in special strengths, packaged in smaller dose sizes, dye-free and preservative-free when possible. Hospitalized children frequently require intravenous medications, and in many cases, fewer alternatives exist for them when a drug is in short supply. For these reasons, the expertise of pediatric practitioners who are familiar with the nuances and intricacies of the care of children must be included in developing solutions for shortages.

Finally, I would like to conclude by recognizing that the underlying causes of drug shortages are complex. Solutions offered today will not solve the many reasons drug shortages exist and continue to increase in frequency. Before enacting legislation focused on addressing these underlying factors, I urge you to carefully and comprehensively study and understand these factors and the downstream impact of any proposed solutions with input from healthcare professionals and other stakeholders. We must return to a state that used to exist when I was a younger practitioner, a state when we had a consistent, reliable, and safe supply chain of needed pharmaceutical products. Nothing less is acceptable.

Thank you for your dedication to this issue and for allowing me minutes to speak as a provider and caregiver representing children

throughout this country who have been affected by these shortages.
Thank you.

[The prepared statement of Mr. Greene follows:]

Drug Shortages & the Need for Action
February 9, 2012
Bill Greene, PharmD, BCPS, FASHP
Chief Pharmaceutical Officer
St Jude Children's Research Hospital
Memphis, TN

Summary of Testimony:

- The challenges that drug shortages are causing for patients and caregivers at St Jude and throughout the country are described
- The case of Lucy, a 5-year old brain tumor patient from Covington TN, is described to illustrate the patient impact of shortages
- The frequency of shortages has increased dramatically. From August 2008 to January 2012, St. Jude experienced a 10-fold increase in the number of shortages which required action
- Drug shortages make it difficult to provide the best possible **patient care**. Shortages cause delays or termination of **research** in important fields like pediatric oncology, including at least 85 Children's Oncology Group (COG) clinical trials. Shortages add **real costs** to the health care delivery system.
- Congress is urged to pass legislation (H.R. 2245 and S. 296) immediately to give the Food and Drug Administration (FDA) the tools it needs to prevent and minimize the impact these drug shortages have on pediatric care and research.
- Congress must give the FDA the resources and authority it needs to combat drug shortages in a proactive manner. Other relevant federal agencies, such as the DEA must collaborate with the FDA to combat drug shortages.
- Congress must ensure that in any solution it develops, pediatric protections are built in and pediatric experts are broadly engaged.
- The underlying causes of drug shortages are complex. Before enacting legislation to address those factors, Congress should carefully study and understand these factors and implications of proposed solutions

Chairman Pitts and other members of the Committee, I am grateful for the opportunity to speak before you – not only as a representative of St Jude Children’s Research Hospital, but as a representative of caregivers at children’s hospitals throughout the country. As you know, I am Chief Pharmaceutical Officer at my organization. St Jude is committed to developing research that leads to new cures for children with catastrophic diseases, and to providing unsurpassed clinical care of these patients. Thank you for letting me address you today.

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.

In my short testimony today, I’d like to share 3 ways Congress can alleviate drug shortages for the pediatric community, but first I would like to begin by putting a face to my discussion. This is Lucy – a 5 year-old from Covington, TN. She and her family have given me permission to describe her case as a way of illustrating the challenges that drug shortages are causing for patients and caregivers at St Jude and throughout the country. Lucy is being treated for medulloblastoma – a type of brain cancer, and today she is doing well. Last spring, she was going through her prescribed course of therapy – supported through her treatment by the administration of intravenous nutrition. She began to deteriorate with blurred vision, random eye movements, and some visual changes; her family and physicians worried that her cancer was relapsing. She was admitted back into the hospital for evaluation. During this workup, her

physicians considered whether all of her new symptoms might be due to a simple vitamin insufficiency. She was treated with intravenous thiamine, and experienced a dramatic recovery and was able to continue treatment.

What was the cause of Lucy's thiamine deficiency that resulted in admission to the hospital? Due to a drug shortage, her care team had been unable to add multivitamins to her nutrition solution for weeks – multivitamins containing thiamine. Despite all our efforts, there simply was no multivitamin solution available to be purchased. As a result, Lucy and her family worried about a relapse of her cancer, and she had to be readmitted to the hospital. This is unacceptable, and this is only one of many shortages that St Jude and other pediatric hospitals around the country have experienced in recent years.

You are aware that the number of drug shortages occurring in the United States has increased dramatically in recent years. A total of 267 shortages were noted in 2011 by the University of Utah Drug Information Service, up from 211 in 2010, which was dramatically higher than in previous years. While not all of these shortages have directly affected St Jude, our hospital has experienced a dramatic increase. **Figure 1** illustrates the number of drug shortages that have affected us since 2008; you will notice a 10-fold increase in the number of shortages which required action at St Jude. In the last 2 months alone, I have had to issue 14 different communications to clinical staff regarding shortages affecting our patients, and all of these notifications involved injectable sterile products. While chemotherapy drugs constitute a significant proportion of the affected drugs, many other types have been affected, including nutritionals, IV electrolytes, antibiotics, anesthesia drugs, and many others.

Drug shortages threaten our nation's healthcare system in three distinct ways. First, we know that we cannot always provide the best possible **patient care**, especially pediatric care for our most vulnerable patients like Lucy, who was dependent on injectable nutrition. Second, we know that shortages cause delays or termination of **research** in important fields like pediatric oncology, including at least 85 Children's Oncology Group (COG) clinical trials. And third, we know that all this adds **real costs** to the health care delivery system, as it did when Lucy had to be admitted for an extra stay at the hospital.

Patient care is affected because patients cannot receive medications that are necessary to most effectively treat their disorders. 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 about 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.** These frequent shortages insert additional and unnecessary complexity to curing children with ALL and other cancers.

While chemotherapy drug shortages have been an area of focus for St. Jude, shortages of other drugs important to pediatric patients have equally important implications. Drug shortages have most frequently occurred with sterile injectable drugs, which are often among the most complex and high risk therapies used in the hospital setting. Shortages of these products only add further

complexity to the use of these therapies and put patients at risk for a new source of medication errors and patient harm. For example, drug shortages often cause frequent shifts to alternate therapies and switching between available drugs, which can lead to errors and adverse patient outcomes.

When St. Jude opened in 1962, only 4% of children with ALL survived. About 90% of children with ALL are cured today due to discoveries made through basic and clinical research. Clinical research at St. Jude and across the country is negatively impacted by drug shortages.¹ 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 and additional work 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.

Drug shortages add costs to the system in many ways. Selection of alternative therapy may result in use of drugs that are more expensive than the originally selected drug. Errors may require additional hospital stay or require unplanned admissions. At the very minimum, busy clinicians devote literally thousands of hours to gather information on shortages, assess the organization's specific situation, create and plan, and communicate this to colleagues.

Obviously, this work does little to improve health care and diverts effort away from important patient care and research activities.

Now, I know that the Subcommittee has likely heard similar testimony before from others. Much data on drug shortages has been shared, and many hearings have been conducted. It is now time for immediate action. So I have 3 points I'd like to make about what Congress can do to help.

First, I urge Congress to pass legislation immediately to give the Food and Drug Administration (FDA) the tools it needs to prevent and minimize the impact these drug shortages have on pediatric care and research. Despite extremely limited resources, the FDA has been effective in minimizing the impact of drug shortages when appropriate communication is made to the agency. Despite a largely voluntary reporting system FDA's efforts avoided almost 200 shortages in 2011., Congress can strengthen the reporting system by enacting H.R. 2245 and S. 296, to give the FDA more complete knowledge of permanent and temporary supply chain disruptions in advance. Once that early-warning system is in place, the FDA can streamline its communication with pharmacists like me so that I can more effectively work to mitigate the impact of drug shortages on patients like Lucy at St. Jude.

These resources should specifically include:

- **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. FDA has proven its ability to avoid shortages in recent years. In 2010, FDA averted 38 shortages when manufacturers voluntarily communicated potential issues, and as already noted FDA avoided nearly 200 shortages in 2011. In a September 2011 FDA Public Workshop on drug shortages, FDA officials noted that additional information from manufacturers has been critical to their improved efforts to prevent shortages.ⁱⁱ

- **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 shortagesⁱⁱⁱ 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.

Second, I urge Congress to give the FDA the resources and authority it needs to combat drug shortages in a proactive manner. While the FDA’s efforts have been laudable, these efforts have been largely reactive and once a shortage has evolved, patients **will be** affected. The agency must have what it needs to develop proactive approaches to predict and prevent shortages before they affect organizations like St. Jude and patients like Lucy. The FDA should have sophisticated systems in place, such as a database of all foreign and domestic manufacturers producing critical

medications, and should develop the ability to forecast supply and demand levels. This technology exists in the private sector and should be expanded nationwide to enable the FDA to work more proactively with suppliers and purchasers to prevent shortages from ever occurring.^{iv} Further, other relevant federal agencies such as the DEA must collaborate with the FDA to combat drug shortages. At the end of calendar year 2011, St. Jude experienced serious drug shortages of controlled substances such as intravenous fentanyl, and concerns have been expressed that the DEA quota system may be inflexible and contribute to drug shortages.

Third, Congress must ensure that in any solution it develops, pediatric protections are built in and pediatric experts are broadly engaged. Children are not just small adults; rather they need specialized care and medications. Children require medications in special strengths, packaged in smaller dose sizes, dye-free and preservative-free when possible. Hospitalized children frequently require intravenous medications, and as you know the majority of drug shortages have been sterile injectable medications. In many cases, fewer alternatives exist for children when a drug is in short supply. For these reasons, the expertise of pediatric practitioners who are familiar with the nuances and intricacies of pediatric care must be included in developing solutions for drug shortages.

Finally, I'd like to conclude by recognizing that the underlying causes of drug shortages are complex. I have offered three possible solutions today that will help address this growing public health crisis in the United States. These solutions alone will not solve the many reasons drug shortages exist and continue to increase. Before enacting legislation to address those factors, I urge Congress to carefully and comprehensively study and understand all the underlying factors

and implications of proposed solutions, with input from health care professionals and other stakeholders. Remember that data from the FDA and other sources point to two major factors as the most common underlying contributors to shortages: manufacturing issues, and quality issues resulting in temporary closure of production facilities.

We must return to a state where a consistent, reliable, and safe supply chain of needed pharmaceutical products exists to protect patients like Lucy. Nothing less is acceptable. Thank you for your dedication to this issue and for allowing me these few minutes to speak as a provider and caregiver, representing children throughout this country who have been affected by these shortages.

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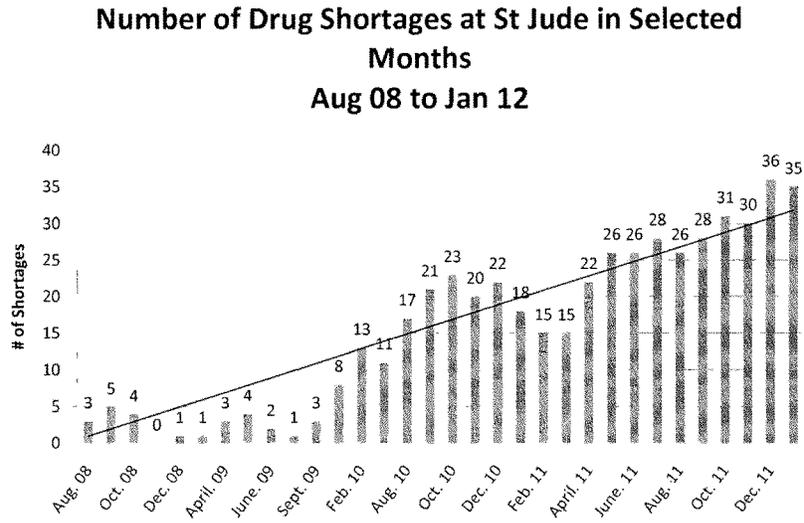
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Figure 1: Drug Shortages Affecting St Jude Patient Care



Mr. PITTS. The Chair thanks the panel for your opening statements. We will now go to questioning, and I will recognize myself for 5 minutes for that purpose.

Ms. Bresch, how will the Generic Drug User Fee Agreement bring predictability and efficiency to FDA's review of generic drugs?

Ms. BRESCH. Thank you. As I think you have heard this morning, especially through Dr. Woodcock's testimony, the need for the resources to truly globalize the FDA is of utmost importance. So as I mentioned, the fact that the generic industry stepped up to provide those resources, the fees are split primarily in two buckets, about 70 percent going towards the inspection and fees for facilities and about 30 percent for the applications. So we believe that with the goals and the metrics laid out in GDUFA that that parity, not just from a timing perspective but also the rigor at how inspections are performed because, you know, I can tell you as having facilities around the world inspected by many regulatory agencies, the FDA does have the gold standard and I think it is very important to raise the bar for the rest of the world, not let the United States' bar come down.

Mr. PITTS. Will this predictability and efficiency bring down the cost of generic drugs and what are the metrics that are included in the goals letter to ensure that progress is made on the review of generic applications?

Ms. BRESCH. So as we have noted, that approval time today for generic drugs is about 31 months, almost double that in recent years. So the goals the metrics laid out bring that back down to about 10 months within 5 years. So it certainly keeps the competitive nature of our industry very much at the forefront while, as we level that playing field, making sure that it is not just competition at any cost. I think what is important to remember is that the competition is important if everybody is held to the same standard. So the certainty comes with the reduction of approval time but making sure that we are having good competition, not just any competition.

Mr. PITTS. Mr. Gaugh, why is the new Biosimilars User Fee Program important to the generic industry and to patients and what are the metrics included in the goals letter to ensure that progress is made in that regard?

Mr. GAUGH. Well, it is extremely important to the American public to have access to the biosimilar pathway of products. As you heard Dr. Woodcock say today, today is the first day that they have announced that they are going to release the guidelines for the biosimilars. So unfortunately, until we see those guidelines, it is going to be hard for me to answer the rest of the question. But it extremely important to have that affordable access to the American public. And you will find that many of the companies that GPhA represents already have these products produced and approved in foreign countries, both Europe and other markets.

Mr. PITTS. Thank you.

Dr. Greene, talk a little bit about how drug shortages affect St. Jude and how many drugs used at your hospitals regularly go into shortage.

Mr. GREENE. Thank you for that question. We deal with shortages on a continual basis. I believe Mr. Engel referred to Montefiore and the number of hours that they have dedicated to

managing drug shortages. I believe you have mentioned 100 or 120 hours per week of total personnel time. That is not a gross exaggeration in any form or fashion. As I mentioned, I am continually engaged in interacting with my clinical staff on what are the shortages, what are the alternatives, when we have fentanyl, when we don't have fentanyl, when we have Zofran, when we don't have Zofran, when we have multivitamins, when we have mannitol, what are we doing when it goes away. It has a dramatic impact and it diverts significant resources away from actually taking care of the patients because we are focusing on one of the most basic elements of care and that is simply do we have the product available for us? So it is a very dramatic impact on us on a day-in, day-out basis. Some days are better than others but some days are simply very traumatic in trying to provide that care.

Mr. PITTS. Can you walk us through, Dr. Greene, what happens from your perspective when there is a drug shortage? Who notifies you? How much warning do you get? What do you need to do to notify people in your organization? Is there any way at present to anticipate a shortage and what preparations do you need to put in place at the hospital level?

Mr. GREENE. You know, I made reference in my testimony the need to support the proposed legislation that effectively builds the tools to allow for early warning types of systems. Historically, we are not aware of a drug shortage evolving until we simply place an order, we check our inventory when it comes in, and we realize after 1 day, 2 days, or 3 days, we keep getting shorted on the order. We don't know about it. Nobody tells us the shortage is there. So effectively, you place an order, you get the drug or you don't, and of course, the shortage is recognized when we don't get it the day after we order it. We place another order, again we are shorted in it, and then finally you begin to realize there is something going on here.

Now, fortunately, at the University of Utah Drug Information Center and American Society of Health System Pharmacists now have a very useful tool that allows organizations to become aware of the experience of other organizations healthcare systems that have experienced shortages so that, for example, I might report to that system that we are having trouble getting methotrexate and that might be the first notification that we are beginning to see problems with methotrexate in the country. And that way other organizations become aware of that. So there is no warning in too many cases and we simply have to be reactive in dealing with those problems.

Mr. PITTS. OK. The Chair thanks the gentleman and now recognizes the ranking member for 5 minutes for questions. Mr. Pallone?

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask a question, Ms. Bresch first, if I could. In your testimony, you emphasized that the imbalance of inspection requirements between U.S. and foreign manufacturing facilities creates an uneven playing field for pharmaceutical plants in the U.S., and certainly one way to help level the playing field, which was mentioned by our previous panel, is to apply a risk-based oversight system to all manufacturing facilities, both foreign and domestic. However, my question is to ensure real parity for all manufac-

turing locations, do you think that a minimum inspection frequency is also necessary and should that be defined in the statute that we would pass.

Ms. BRESCH. I believe that risk-based is appropriate but I do believe that defining how that risk-based works is incredibly important. I mean if I give the example—I talk about our facility in Morgantown, West Virginia. There are two full-time employees by the FDA who live in Morgantown, West Virginia, for just our facility. So if the risk-based is not defined properly, our concern is that it will be easy to go to where FDA has been going and that compliance-based will be extremely important to define that formula. So I believe that the legislation needs to have a very well defined formula and that there should be some minimum that a facility would need to have been inspected by.

Mr. PALLONE. OK. Thank you.

Let me ask Mr. Gaugh, I am interested in this Accelerated Recovery Initiative, or ARI—I mentioned it previously also, I think before the last panel—that you described in your testimony. It sounds like a promising effort that would help industry address or prevent shortages, and I am interested in hearing exactly how it would interface with the FDA. Could you explain what the role of the FDA would be in that initiative and particularly I would like to learn what the third party would be able to do that the FDA does not do and whether you see this initiative as potentially complementary to legislation that would mandate FDA notification? Or is it your hope that it would be instead of legislation?

Mr. GAUGH. Thank you. From the standpoint of pulling this together, as I said earlier in my verbal testimony but also in the written testimony, this will be a multi-stakeholder event. And there are many questions that were asked of Dr. Woodcock that would be addressed by the ARI. For example, as we were talking about the gray market and I can't remember—I think it was Mr. Cassidy that asked about how we know how much product different organizations, a hospital can get when they order or how much is available to them. That would mean that in this ARI, the key stakeholders would be the manufacturers, the wholesalers and distributors, purchasing organizations, the FDA most importantly, and then the third party, as you mentioned, which would be an independent third party.

The issues that we have addressed in the small group that is pulling the ARI together is that this is a very competitive marketplace, of course, and it would be fraught with some FTC potential issues if not handled in an appropriate fashion. So the appropriate fashion that we have come up with to this point is an independent third party that will be a blinding party if you will so they are the only party that sees all information coming from all the competitive companies.

To answer your question about why the FDA couldn't perform this, there are multiple reasons. One, it isn't currently in their responsibility of duties as you see the responsibilities. Number two, Dr. Woodcock talked about the limited resources they currently have, which is very true. The drug shortage was only four or five people up until a few months ago. It has now been doubled, I believe, to seven or eight people. So that would be a limiting factor.

The other piece is the third party is going to have to be somebody who really understands production planning extremely well and can take production planning reports from the multiple different companies to make determinations and decisions on who could or who could not produce products to help alleviate this drug shortage. That is not something that currently exists within the—

Mr. PALLONE. Just because I am running out of time, it sounds to me that in terms of the question I asked that you are saying that the initiative, the ARI is complementary to legislation that we would initiate. In other words, not that it would be instead of, but because of the need to work together and certain things that can't be done, this would have to be something that we would have to work out in terms of the legislation. Is that accurate?

Mr. GAUGH. That is correct. That is accurate.

Mr. PALLONE. OK. All right. Thanks so much.

Mr. GAUGH. You are welcome.

Mr. PITTS. The Chair thanks the gentleman, recognizes the vice chairman of the committee, Dr. Burgess, for 5 minutes for questions.

Mr. BURGESS. Thank you, Mr. Chairman.

And Mr. Gaugh, if I could stay with you for a moment. And let me just ask you and I know this is a wide-ranging question so I am going to ask you to be as brief as you can, but in your opinion, what are the reasons that a drug goes into shortage?

Mr. GAUGH. I am sorry. Can you repeat—

Mr. BURGESS. What are the reasons that a drug goes into shortage?

Mr. GAUGH. Dr. Woodcock described the overall situation with drug shortage, so it really is a demand versus supply situation right now. So the demand continues to increase in the United States with the graying of America, et cetera. So demand continues to go up. The currently available supply is going down, so as she talked about in the injectable industry in particular, there is a defined quantity of production capability in the U.S. Currently, most of the companies that are under the production capability piece are in remediation efforts due to their compliance or their lack of compliance situation. So the available capacity today is less than it was about a year and a half ago.

Mr. BURGESS. And here is the thing. The manufacturing processes in many of these drugs are not new. They have been around for a long time. The FDA has been doing inspections for years. The companies have had to get the raw materials for years. They have been making injectables for years. So why the acceleration in the last 5 years?

Mr. GAUGH. If we are still just talking about sterile generic injectables, the basic five companies that have the majority of the production capability, these are aged facilities. So as the manufacturing lines are becoming older, they need to be replaced, refurbished, upgraded. Specifically, also, the specifications, the criteria that need to be met are changing year after year. Those have to be implemented. Sterile injectable production is a very complex process. It takes time to upgrade those systems, and when you do upgrade them, you have to take them down for a period of time.

Mr. BURGESS. Right. But don't you find it odd that it really has been a snowball effect? I can remember in the 2004 presidential election, in one of the debates that fall, flu vaccine had been contaminated with serratia. We got it from an overseas source and President Bush was just pummeled for this flu vaccine shortage. And now the shortages are happening all the time. That level of scrutiny doesn't seem to be being applied to the fact that more and more drugs are drifting off into a shortage situation. Why is that?

Mr. GAUGH. Because I would say the level of scrutiny that is upon those companies by the FDA has increased over the last 3 to 4 years, and that level of scrutiny is what—

Mr. BURGESS. But the shortages are going to be manifested by the clinicians not having the compound to deliver to their patients, not the Food and Drug Administration saying aha, we have identified a shortage in your line. It is because at the end of the line, the doctor and the patient are saying I can't get this stuff. So let me ask you this. There are some new branded drugs that are complex molecules, difficult to manufacture, and there are 10 to 15 generic oncology drugs that have been around forever and are quite basic in their formulation, and those are the ones that are in shortage, not the complex new molecules. So why is it that the complex branded drugs are readily available and the basic generic drugs are in short supply?

Mr. GAUGH. Typically, the complex brand molecules you are talking about are manufactured in one facility, one line for that particular product. Or do you look at the generic injectables. Those companies produce anywhere from 50 to 120 different molecules on their different lines. So it is a supply-and-demand issue again within that facility of the number of products that are made.

Mr. BURGESS. I brought this up in my opening statement. Do you think there is the possibility that we have perhaps made things a little too tight, made the margins a little too tight where it is difficult for companies to justify continued manufacture if they have a difficulty in their manufacturing process or for other companies to step in and fill the gap if a company has to withdraw from the manufacturing?

Mr. GAUGH. In the market—

Mr. BURGESS. We just don't have the profit margins built in under current constraints?

Mr. GAUGH. Profit margin could be one of the causative effects, but it is not one of the major causative effects, no.

Mr. BURGESS. OK.

Mr. GAUGH. It is still a demanding market in the U.S. and you can change the price as needed.

Mr. BURGESS. Very well. Dr. Greene, let me just ask you a question. You heard Dr. Cassidy on our side, you heard Lois Capps on the other side of the dais reference what they suspect was a problem in the gray market where some hospitals might be buying up a compound that is going into shortage and then reselling it at a much higher markup. I mean Dr. Cassidy has some specific questions. You deal in hospital purchasing all the time. Was he on the mark there or was that off?

Mr. GREENE. Someone certainly is getting product somewhere and, you know, maybe it is an entrepreneurial way, but they are

taking advantage of shortages to make dramatic markups. Now, how they get the product, I don't know. I would be very, very surprised if any hospital is actually purchasing it for the purpose of diverting it to the gray market. We know that it happens; we just don't know where these individuals get their drug. And that is one of the reasons why St. Jude, we do not purchase off of a gray market.

Mr. BURGESS. Well, where would be a more likely place to look, then, if it is not the hospital purchasing?

Mr. GREENE. I wish I could explain that. I don't know. I know that there are thefts. There are reports of tractor-trailer loads of drugs that have been simply stolen and you don't ever know where those go and how they get into the marketplace and so I simply do not know where those drugs come from.

Mr. BURGESS. You agree that it is a problem?

Mr. GREENE. I don't know that it contributes dramatically to shortages. I think it is a problem in the context that it provides potentially very expensive and potentially harmful products for use in patients.

Mr. BURGESS. All right. Thank you for your time.

I yield back, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and yields to the ranking member emeritus, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you.

These questions go to Ms. Bresch. First I want to welcome you to the committee. Thank you. And second, I want to thank you for your leadership in this matter and tell you how much it has meant to me. These questions will be all yes or no. Do you agree that both FDA and the industry have a responsibility to ensure the security of our drug supply chain? Yes or no?

Ms. BRESCH. Yes.

Mr. DINGELL. Do you agree that the knowledge of your suppliers is important? Yes or no?

Ms. BRESCH. Yes.

Mr. DINGELL. Does Mylan have systems in place to know their suppliers and monitor manufacturing quality? Yes or no?

Ms. BRESCH. Yes.

Mr. DINGELL. It would be nice if you had more assistance in this, however, from FDA, would it not?

Ms. BRESCH. Yes.

Mr. DINGELL. Does Mylan have systems in place to demonstrate quality control? Yes or no?

Ms. BRESCH. Yes.

Mr. DINGELL. Should all companies making drugs for the United States know their suppliers and have quality systems in place?

Ms. BRESCH. Yes.

Mr. DINGELL. Should all companies making drugs for the U.S. be able to demonstrate quality control? Yes or no?

Ms. BRESCH. Yes.

Mr. DINGELL. Should companies be using risk analysis to target safety risks? Yes or no?

Ms. BRESCH. Yes.

Mr. DINGELL. Do you need to have the same kind of attention given to the supplies and the commodities and the other things that go into the pharmaceuticals that you sell as finished products?

Ms. BRESCH. Yes.

Mr. DINGELL. Do you agree that strong quality management systems and risk analysis will help companies to ensure the safety and quality of the finished drug product?

Ms. BRESCH. Yes.

Mr. DINGELL. I want to turn now to inspections. The brand industry has noted that its user fees go to pay for a preapproval inspection which could include an inspection of a foreign facility. Is preapproval inspection the same as a GMP inspection? Yes or no?

Ms. BRESCH. No.

Mr. DINGELL. Please explain the difference.

Ms. BRESCH. The way PDUFA was written and is implemented is really focused on the speed for an individual product. So a preapproval inspection is on a certain product which could be made on one line in a facility, and once that product is approved, it would never require the FDA to come back and inspect that line. GMP inspection covers the entire facility and ensures that that facility is complying to good manufacturing practices.

Mr. DINGELL. And you do desperate need Food and Drug to come back for that purpose to ensure that good manufacturing processes are being carried out at the plant being inspected. Is that right?

Ms. BRESCH. Absolutely. I think as we have heard a lot today, the vigilance that is required is on an ongoing basis. Just because you meet GMP inspection or are GMP compliant, that does not mean you are GMP compliant for the rest of that facility's life. And that is why earlier when asked about a risk-based approach to inspections and that we still believe that there would be a minimum number of years that the FDA would need to be back in that facility because it requires ongoing constant vigilance.

Mr. DINGELL. Now, you stated in your testimony that the Federal Food and Drug and Cosmetic Act should be updated to require parity of inspections for domestic and foreign facilities. Why does Congress need to change the statutory language when FDA has already agreed to do on a voluntary basis in the Generic Drug User Fee Act?

Ms. BRESCH. Well, and I want to thank you for your leadership in this area for many years. I think to have an agency as important as the FDA to be governed by a 1938 law that was written from a very domestic standpoint and yet we are needing and demanding the FDA to govern a global industry. So if we are not going to have the global industry return to a domestic one, we have no choice but to have the 1938 law be representative of the world that the FDA needs to operate in today. I think we heard Dr. Woodcock speak about the fact that there is just a different standard. For products manufactured in the United States, it is assumed to be adulterated unless proven that it has been made to GMP, yet if we are importing drugs, the standard that we hold those imports to are we have to show and prove that they are not up to GMP or we have to let them in. So I believe that that 1938 law desperately needs—

Mr. DINGELL. To be changed.

Ms. BRESCH [continuing]. To be updated so that the FDA has all the ability to make all the decisions and necessary demands to ensure the safety in the supply chain integrity on a global basis.

Mr. DINGELL. Now, it is also grossly unfair to surround American manufacturers with all these requirements while literally FDA is able to surround foreign manufacturers with virtually none, isn't that right?

Ms. BRESCH. Absolutely. Again, we talk about the competitive nature of this industry, so we are forced to compete really at any cost. So we are competing every day from competition and companies around the globe that perhaps don't hold their facility to the same standard as we do. We have facilities all over the world, as I mentioned, that make product for the United States and we hold all of our companies to the same GMP whether that facility is in the United States or outside of the United States. So the need for the competitiveness as a U.S. manufacturer is very unlevel at the moment, and unfortunately, as a manufacturer who employs many American jobs, like I said, we would like to not only maintain those but to increase them. And right now we are disincentivized to do so.

Mr. DINGELL. Mr. Chairman, I have used all my time but could I have one more question?

Mr. PITTS. You may proceed.

Mr. DINGELL. Ma'am, the Generic Drug User Fee Act Agreement is unique in that it recognizes that FDA needs new resources and new authorities to properly oversee what is now a globalized industry as you have been pointing out to us. I happen to believe that the Food, Drug, and Cosmetic Act should and needs to be updated to reflect the global nature of our drug supply, again as you were pointing out, and to adequately equip FDA with the authority to properly ensure the safety of our drug supply, and that would include the commodities that go in an unfinished state. This committee has worked in a bipartisan manner to secure the safety of consumer products in our food supply, and I hope that we can do so for pharmaceuticals.

I want to commend you for what it is you have done today and for your guidance and counsel in these matters. It has been most helpful and you go with my thanks and I think the thanks of the committee.

Mr. Chairman, thank you for your courtesy.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman from Illinois, Mr. Shimkus, for 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. Again, I do appreciate the panel and your time today.

Ms. Bresch, you are from West Virginia, is that correct? I mean the facility is in West Virginia, is that what you said?

Ms. BRESCH. That is where our largest facility is. We have facilities all over the United States.

Mr. SHIMKUS. OK. Do you know how many drug manufacturing facilities are in the State of West Virginia?

Ms. BRESCH. I don't know of any other.

Mr. SHIMKUS. At the West Virginia facility, there are two FDA inspectors 24/7?

Ms. BRESCH. They live in Morgantown, yes.

Mr. SHIMKUS. And they are dedicated solely to your facility?

Ms. BRESCH. I can't speak to what they are dedicated to but I can tell you that they live in Morgantown, West Virginia, and like I said, we are the only pharmaceutical company—

Mr. SHIMKUS. I mean, do they come in every day to your facility?

Ms. BRESCH. They are not necessarily in our facility every day so that is why I am saying I am sure the FDA can utilize them in other manners. My point is being that we have countries that don't have an FDA employee, so when you think about Morgantown having two, it can just demonstrate the unlevel playing field.

Mr. SHIMKUS. Yes, I would like to have two in China maybe.

Ms. BRESCH. Or maybe 200, but yes.

Mr. SHIMKUS. Yes, at least two would be a start.

Ms. BRESCH. Exactly.

Mr. SHIMKUS. But I think that raises an issue and I do appreciate your comments. I have been focused on this risk-based system for a long time and it is not to walk away from U.S. facilities but it is to recognize the fact that as Chairman Emeritus Dingell said, I mean you had an inspector onsite, you have got programs and plans and systems to obviously check that yourself. We also have a pretty good litigious environment that also keeps U.S. Manufacturing facilities somewhat cognizant of the safety and efficacy of what they are doing in the facility. So I think there would be, if we did aggressively move in a risk-based approach, there would be a return. It is not like they are never going to come back to Morgantown, West Virginia, and check in on you.

Ms. BRESCH. And we want them to. And I think that is the point of the vigilance that I spoke about. It is that need, you know, we say all the time there are good actors out there and bad actors everywhere, United States included. It is just the rigor that the FDA has to inspect the U.S., we find those quicker or perhaps never in some other countries.

Mr. SHIMKUS. Thank you. Dr. Greene, I apologize for you not getting your charts and stuff up on the overhead because we were able to pull it from your testimony. And this is pretty stark. And I would guess you are pretty concerned that trend line is not changing any time soon, is that correct?

Mr. GREENE. It doesn't portend good things for the future if it continues in the same direction.

Mr. SHIMKUS. And so from the other members in this discussion, it seems like we kind of mealy-mouth around trying to really identify the problem. We talked about this in the last hearing and I was just asking a basic question because I am a conservative competitive market corporate Republican, believer in supply-and-demand principles. Why is that not working here? Why isn't there a signal being sent to manufacturers, hey, there is a demand that is not being filled. Can you not send a price signal—

Mr. GREENE. Right.

Mr. SHIMKUS [continuing]. That would then generate an interest, especially as Dr. Burgess said. Some of this stuff isn't really the high-tech type stuff. I mean when the mention of saline solution with vitamins inside of it you are thinking he is telling me that, that stuff we do all the time. For that to be a limited availability, that is crazy talk.

Mr. GREENE. Yes, I am not qualified to really comment on whether the economics are dramatically a part of this or not. I would leave that to the economists. It would seem to me that—

Mr. SHIMKUS. Well, let me ask if anyone else can talk—I mean part of hearings is trying to find an answer. So go ahead, Mr. Gaugh.

Mr. GAUGH. So economics can be a piece of it, absolutely, but are they the driving factor? They are not the driving factor.

Mr. SHIMKUS. OK, when you say the economics could be, so drill down a little bit.

Mr. GAUGH. So in drilling down a little bit, the economics, yes, if a product in the competitive market space went down so far that there was no more margin, you would make a decision potentially to get out of that market, but this is a free market environment and you can raise that price back up and get—

Mr. SHIMKUS. That is what I would assume but it doesn't seem that the market signals are being sent when there is a limit that the price is going up to encourage people that are in the market.

Mr. GAUGH. Right. And the issue we are talking about now is sterile generic injectables. When you look at that line on the graph that he had, the majority are those. It is purely a capacity limitation to be able to produce those products.

Mr. SHIMKUS. So the market signal would send if they can get a return on investment, it would send a signal to the manufacturers, expand to meet the demand, but the signal is not being sent.

Mr. GAUGH. It is being sent but expand is a 7-year proposition typically from the day that you—

Mr. SHIMKUS. OK. But why is that?

Mr. GAUGH. The day you break ground until you are approved by—

Mr. SHIMKUS. Rules, regulations, siting, permitting, all this other junk?

Mr. GAUGH. The FDA approval is an 18-month process—

Mr. SHIMKUS. There is a—OK.

Mr. GAUGH [continuing]. And that is just to get the site approved and then to move the products into that site is an additional—

Mr. SHIMKUS. Well, and that is a great—and my time has expired, Mr. Chairman, and I appreciate it, but I think that is where some of this debate needs to be. How do we move aggressively, safely to allow expansion to meet these shortages? Because this is ridiculous and we shouldn't put up with it. And I yield back my time.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman from New York, Mr. Engel, for 5 minutes for questions.

Mr. ENGEL. Well, thank you. Thank you, Mr. Chairman.

Mr. Gaugh, I want to follow up on something that Dr. Burgess mentioned before. In your written testimony, you stated that your trade association acknowledged that roughly half of all reported shortages are associated with manufacturing problems. Why do you believe that there has been such a significant increase in manufacturing-related issues in recent years and can you please elaborate on what steps the manufacturers of generic medications are taking to address this problem? Obviously, we cannot neglect patients' safety and so it is a matter of great concern.

Mr. GAUGH. So if I understand your question correctly, you look at the environment today—and again I am going to focus on the sterile generic injectables—roughly 25 to 30 percent of the currently available capacity is not available for production due to remediation efforts. So if you take that 30 percent roughly out of production, that is the majority cause of these drug shortage situations.

Mr. ENGEL. All right, thank you. Dr. Greene, you had commented on a comment I had made involving Montefiore Medical Center having to take hours to, you know, make sure the things are ameliorated. I want to give you a chance to elaborate on that a little more.

Mr. GREENE. Specific to St. Jude I presume?

Mr. ENGEL. Yes.

Mr. GREENE. Yes, one of the things we have simply developed is a standard practice every week is one of the questions we do in our routine administrative discussion is what is our latest state of drug supply issues? What are they? What is their acuity? Do we move them out into the clinical discussion realm or is this one that we work within the pharmacy? I have literally three individuals that are routinely engaged in the discussion and evaluation and follow up to me every day. That is not all that they do but they spend a significant amount of their time dealing with these issues. And part of the problem from my point of view is the volatility in the supply. I have fentanyl today; no, I don't have fentanyl tomorrow. It is back. I only have large-volume files. I don't have small volume. Well, I have got single-dose vials this week but I don't have the vials that I need to use to make PCAs. So those are the kinds of issues that we are dealing with at any given time.

Mr. ENGEL. Thank you. I mentioned to Dr. Woodcock, I had asked her this question that many of you mention in your written testimony that the user fees included in GDUFA and BsUFA are meant to be in addition to a solid base of annually appropriated funds of the FDA. In fiscal year 2012, the FDA received a 50 million increase in funding, which was a very big victory for those of us who felt that happen because the first proposal was a \$285 million cut in FDA funding for fiscal year 2012. So would any of you care to elaborate on why it is so important that the FDA be adequately funded and how cuts to the FDA could impact your industry or the patients your associations serve?

Ms. BRESCH. I will speak to that. I think that as Dr. Woodcock mentioned the premise has always been the FDA would have the appropriations and that they would never solely rely on user fees for any particular industry. And that is why I think as you see the GDUFA being, you know, a very novel and landmark user fee, the Agency has obviously funded the Office of Generic Drugs since 1984 and has been very successful. Hopefully, the user fee is now complementing that. I think that when you look at the need for the Generic Biologics Program, the same does not hold true and I think that is where we run some risk of having it being way too weighted on strictly user fees and not having the appropriate appropriations from the Agency perspective to carry out their mission.

Mr. ENGEL. Thank you. I agree with you.

Anybody else care to—oK, well, then thank you, Mr. Chairman. I yield back the balance of my time.

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

Mr. CASSIDY. If I seem in a hurry, I am missing a lunch with the greatest chefs in Louisiana, so—oh, my gosh, I am tasting the food.

Now, Mr. Gaugh, you mentioned, though, that there is no reason a price signal could not be sent, but there actually are constraints on how 340B will allow a company to raise its pricing. And you will know more about 340B than I but I am struck that this price signal Shimkus is after is dampened by the 340B process.

Now, Dr. Greene, you are St. Jude's?

Mr. GREENE. That is correct.

Mr. CASSIDY. Now, I think I know but correct me if I am wrong that pediatric IV immunoglobulin, because of a shortage, was taken out of the 340B program. One, is that correct? And two, if correct, how has that affected supply?

Mr. GREENE. Well, it is my understanding that that is correct. We have not to my knowledge in the time that we have been engaged in the 340B program, it has only been about a year and a half now I suppose, not quite that long. I don't think we have ever been able to purchase any consistent supplies of IV IG in the 340B program, and yes, I would say that that is true. The supply has been available to us; it is just that we have had to pay the regular market rate defined through our group purchasing organization.

Mr. CASSIDY. So that is interesting. And again, I think IV IG was taken off of 340B pricing. I think that is true. So now the supply is there and it was absolutely taken off because it was never available before. I think I know that but I am a little rusty on my thought.

Mr. Gaugh, you are nodding your head yes. Is that a correct—

Mr. GAUGH. That is correct.

Mr. CASSIDY. I remember that correctly?

So if you will, the restoration of a price signal restored supply. I will just point that out. Now, Dr. Greene, you also mentioned St. Jude's—everybody knows St. Jude's—that you have had a hard time at times in your testimony you said you could not get chemotherapeutic agents. But you all are big so I presume you obtained them someplace. I was kind of interested in the gray market. Do you get them from other hospitals, do you buy them from third parties, do you go into the gray market? I am not asking you to indict yourself but I am trying to understand what do companies do when they can't get this drug?

Mr. GREENE. I can think of two specific examples in the last year, one was cytarabine—we use a lot of that for treatment of our ALL patients—and it got to the point where we had to consider seriously whether we could accept new patients for treatment of ALL.

Mr. CASSIDY. I knew it at the time so if you could cut to the chase, how did you supplement your supply?

Mr. GREENE. Well, we were diligent first on the marketplace to try to find any source but also communicated with colleagues at other organizations. I had other hospitals in the region—

Mr. CASSIDY. Did you ever go on the gray market?

Mr. GREENE. Oh, no. No, we do not buy from gray market.

Mr. CASSIDY. OK. Ms. Bresch, I am struck when I asked in a previous time why don't you just backtrack? OK, here is a hospital that buys on the gray market. Why don't you just take this all the way back and find out where the source of the gray market was? Because different hearing but same topic, oh, we don't know where it is coming from. You don't know where it is coming from? Why don't you just call up hospital X and say who did you buy it from? Now, you are on this end, not that end, but how would you comment upon how we are tracking drugs?

Ms. BRESCH. I think you perhaps just answered your question. We don't track drugs and the FDA does not track drugs and in fact one of the premises of GDUFA, the generic industry proposal was the fact that this has led to a very weak supply chain. So I know there has been a lot of discussion today on drug shortages about is there a price point, what is really the cause of it? And I would contend that one of the issues that we are seeing as a result is this very weak supply chain we have today. So not only do we not track—I mean I believe the FDA would tell you they have no idea where some products are manufactured throughout the world, they have no even idea where the facility is—

Mr. CASSIDY. So when people buy online from oversea pharmacies, we have no clue whether that pharmacy is doing GMP, the manufacturers, or even whether it is counterfeit drug, correct?

Ms. BRESCH. You don't have any idea if you walk into your corner pharmacy here in Washington, D.C. You don't even have to go online. Today, you have no idea where the product you are buying comes from.

Mr. CASSIDY. My jaw drops.

Ms. BRESCH. I couldn't agree more, and that is why sterilization which has been a topic, I know of some other hearings, and the need for us to be able to track and trace, we highly agree that that needs to happen—

Mr. CASSIDY. Now, let me stop just because we have 18 seconds left before I return to my Louisiana seafood, how would you all define the gray market? I am just curious what is a working definition in your mind?

Mr. GAUGH. Entrepreneurial America is how we define it.

Mr. CASSIDY. So you wouldn't see a problem with it or you would just say that—

Mr. GAUGH. Oh, I do see a problem with it, absolutely, but it is not illegal that we are aware of. It is a brokerage firm if you will so it is people—

Mr. CASSIDY. So it is not a black market in the sense that it is legal. On the other hand, it is a gray market created by price distortions and shortages?

Mr. GAUGH. Exactly.

Mr. CASSIDY. Would you agree with that, Dr. Greene?

Mr. GREENE. I would. And there is no pedigree that runs through the gray market process and that is why you can't trace it back through the gray market.

Mr. CASSIDY. OK.

Mr. GREENE. You can trace it to a certain level but not completely because the pedigree doesn't exist in a gray market environment.

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

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

Ms. DEGETTE. Thank you very much, Mr. Chairman. And thank you for the comity that you have given to allow me to question as a member of the full committee.

Dr. Greene, I wanted to ask you what would you be able to do with these patients if you were informed in a timely fashion of an impending drug shortage?

Mr. GREENE. Well, of course, it would depend upon the severity and the shortage and what details would come out of that, but the first step we would assess is the number of patients that would be dependent upon that drug, the number of patients affected, the alternatives that we would have to consider and their relative risk-benefit compared to the first drug of choice that would—

Ms. DEGETTE. Let me ask you this because you said that you were supporting House Bill 2245—

Mr. GREENE. Yes.

Ms. DEGETTE [continuing]. Which gratified me because I am the prime sponsor of that bill—

Mr. GREENE. We are grateful for that, too.

Ms. DEGETTE [continuing]. Along with Congressman Rooney. It is a bipartisan bill that has Democratic and Republican cosponsors, so what that does is it basically expands the current FDA voluntary reporting program and makes it—

Mr. GREENE. Right.

Ms. DEGETTE [continuing]. Mandatory. Who would that help you be able to do your job better in treating these patients?

Mr. GREENE. In short, it would alert us to situations that we could do something about before it reached us. We could modify our dosing approaches; we could take additional steps to minimize waste. You know, there are sometimes alternatives depending on the drug that we could easily switch to before we deplete our on-hand supply. There are a number of on-hand things we could do.

Ms. DEGETTE. Now, you would agree with all of us that this legislation and just doing reporting, that doesn't solve the underlying problems. It just mainly helps you deal with that chart that some folks were showing where you have these terrible shortages and it impacts patient treatment, right?

Mr. GREENE. That is correct.

Ms. DEGETTE. Now, Ms. Bresch, I am going to assume you don't like the idea of drug shortages either, do you?

Ms. BRESCH. No.

Ms. DEGETTE. And I would assume, Mr. Gaugh, you don't like them either, right?

Mr. GAUGH. Do no.

Ms. DEGETTE. And I know, Ms. Bresch, your company right now in fact participates in the voluntary FDA reporting program right now. You have got four drugs, largely injectables, that are right now on the shortage list, right?

Ms. BRESCH. But to my knowledge, our shortage is because we have helped fill the capacity because another manufacturer——

Ms. DEGETTE. Right. No, I am just saying you participated in that program, right?

Ms. BRESCH. Yes, absolutely.

Ms. DEGETTE. And it has worked for you, right?

Ms. BRESCH. Yes, for years.

Ms. DEGETTE. And for years. And what you are suggesting I think is really important, which is if we modified some of the underlying laws that have been on the books for decades and decades, that might help solve the underlying problem of drug shortages, right?

Ms. BRESCH. Absolutely. I believe strengthening the supply chain——

Ms. DEGETTE. Right.

Ms. BRESCH [continuing]. Would go a long way.

Ms. DEGETTE. Right, and expediting the approval process and everything else——

Ms. BRESCH. Absolutely.

Ms. DEGETTE [continuing]. Right? And Mr. Gaugh, you are nodding, too. You think so, too, right?

Mr. GAUGH. Yes, I would agree.

Ms. DEGETTE. But, you know, it is time to start fixing the underlying problems even if we pass legislation right away, which I would support doing that, that is not going to solve the drug shortage issues that Dr. Greene and all the other hospitals are dealing with right now, correct?

Mr. GREENE. That is correct.

Ms. DEGETTE. Yes. And so I know Mr. Gaugh, your association has proposed this Accelerated Recovery Initiative, which would be a voluntary collaboration for the industry to work on some reporting issues, correct?

Mr. GAUGH. Yes.

Ms. DEGETTE. And you are not moving forward with that until you make sure that the FTC has addressed your antitrust issues, right?

Mr. GAUGH. We are moving forward in a parallel path if you will, yes.

Ms. DEGETTE. Right, but if there is antitrust issues, you are going to have to address those. Now, that particular program, it is not either/or with the FDA reporting program, right? You could have both the industry program and the FDA program, right?

Mr. GAUGH. Yes, and it would be in support of it. We have already presented to the FDA and they are in agreement in concept with the process.

Ms. DEGETTE. Yes. And by the way, I am in agreement with the concept, too. I like the concept of having industry having a reporting process but also having the FDA have a reporting process. Now, has your association taken a position on House Bill 2245? That is the legislation that I talked about.

Mr. GAUGH. Not the notification process. We agree with notification; it is the details that would be in that. And——

Ms. DEGETTE. Have you looked at my bill?

Mr. GAUGH. Oh, absolutely, yes.

Ms. DEGETTE. And what is your position on my bill?

Mr. GAUGH. And have spoken with your staffers as well.

Ms. DEGETTE. Sorry?

Mr. GAUGH. And have spoken with your staffers as well, yes.

Ms. DEGETTE. I heard that rumor. And what is your position on my bill?

Mr. GAUGH. We support the communication process as far as industry communicating to the FDA when drug shortages are known. The devil, as I said, is in the details on—

Ms. DEGETTE. What details do you have a concern about?

Mr. GAUGH. The mandatory timing of those, so, you know, the 6-month or the 1-year notification process as long as we are aware of that is appropriate, but in many cases we are not aware—

Ms. DEGETTE. So it is just some technical language that you think we could work out?

Mr. GAUGH. Technical, yes, absolutely.

Ms. DEGETTE. And we look forward to working with you.

Thank you very much, Mr. Chairman.

Mr. GAUGH. Thank you.

Mr. PITTS. The Chair thanks the gentlelady. The Chair thanks panel two for your testimony, excellent information.

That concludes our second panel. And I would like to thank all of the witnesses and members for participating in today's hearing and remind members that they have 10 business days to submit questions for the record, and I ask the witnesses to respond promptly to the questions. Members should submit their questions by the close of business on Friday, February the 24th.

Without objection, the subcommittee is adjourned.

[Whereupon, at 1:09 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

**Opening Statement
Chairman Fred Upton
Subcommittee on Health Hearing
Thursday, February 9, 2012**

Today's hearing on the proposed generic drug and biosimilars user fees and drug shortages is an important part of our broader effort to address FDA drug and device approvals as we work to extend and expand user fee programs well before the September deadline.

The new generic drug user fee and biosimilars user fee would bring resources to FDA to help the predictability, consistency, and transparency of FDA regulation.

Currently, there are approximately 2,500 applications in the generic drug backlog, and it takes about 31 months to get a generic drug application in that backlog reviewed. This backlog is preventing important generics from getting to the market, putting additional financial strain on our nation's patients. Under this proposed user fee agreement, the generic backlog would be effectively eliminated in five years and future applications will be reviewed on a timely basis. I believe the proposed generic drug user fee and associated goals would bring tremendous improvements, and the generic drug industry and FDA deserve credit for their hard work in coming to this agreement.

The biosimilars user fee would bring resources the agency needs to help bring predictability to FDA's review of biosimilars applications. This predictability will help innovation in this burgeoning area.

This hearing also will focus on drug shortages, and I appreciate the chairman's continued leadership on this issue. Building on the hearing this subcommittee had in September, the discussion today will bring additional ideas on how Congress can help. Drug shortages are hurting patients across the country, and I look forward to working on a bipartisan basis to help alleviate the problem. Mr. Walden, Dr. Gingrey, Mr. Bass and Mr. Latta have been particularly engaged on our side of the aisle, and I know Ms. DeGette and others have been active as well.

**Congressman Marsha Blackburn
Opening Statement for Energy and Commerce
Health Subcommittee Hearing
“Review of the Proposed Generic Drug and Biosimilars User Fees and Further
Examination of Drug Shortages”
February 9, 2012**

Thank you, Mr. Chairman.

I look forward to hearing from Dr. Woodcock and our panelists on these two new user fee agreements.

I am extremely eager to continue our exploration of the drug shortage issue and how we can help FDA focus their resources where they can be best used.

I am also honored today to have with us a Tennessean – William Greene from St. Jude Children’s Research Hospital in Memphis, TN.

This year, St. Jude celebrates 50 years of leadership in the areas of pediatric treatment and research. Their discoveries have completely changed how the world treats children with cancer and other catastrophic diseases.

We are grateful to Mr. Greene for joining us today and I look forward to his testimony.

I yield back.

Opening Statement
Congresswoman Cathy McMorris Rodgers
February 9, 2012
Subcommittee on Health
Hearing on The Review of the Proposed Generic Drug and Biosimilars User Fees and
Further Examination of Drug Shortages

Mr. Chairman:

I would like to take this opportunity to clarify aspects of the hearing that imply that the 340B program may have a role in drug shortages, in particular, statements concerning IVIG and its role in the 340B drug discount program.

IVIG is considered a covered outpatient drug under the 340B program, and, therefore, manufacturers are required by law to sell IVIG at 340B prices to safety-net providers. It should also be noted that the Food and Drug Administration has issued a statement that there is "no evidence of an overall shortage of [IVIG] at present, or indicators of an impending shortage."

Concerns have been expressed over the availability of IVIG. 340B hospitals have long been vocal in alerting officials about manufacturers that either decline to sell IVIG at 340B prices or limit the quantity of 340B-priced IVIG or then compel the hospitals to buy the rest of their IVIG outpatient supply at higher, non-340B prices, which violates 340B program guidelines, not to mention the spirit of the 340B program.

In response to providers' concerns about IVIG access, HRSA confirmed in 2005 that manufacturers cannot allocate a drug based on a provider's 340B status. Moreover, Congress created a "must-sell" provision that requires manufacturers to offer each covered entity a drug at or below the applicable ceiling price if that drug is made available to any other purchaser at any price.

Unfortunately, even this clarification has not ameliorated the situation. A 2011 Government Accountability Office report on the 340B program noted that many stakeholders reported continued problems when trying to access IVIG at 340B prices. To address this, HRSA clarified that manufacturers' limited distribution plans must be reviewed by HRSA before the plans are implemented.

I look forward to working with my colleagues, safety-net providers in the 340B program, and IVIG manufacturers and distributors to ensure patient access to this critical treatment.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED TWELFTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115

Majority (2021 225-2927)
Minority (2021 225-3641)

March 19, 2012

Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock:

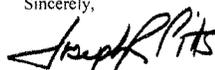
Thank you for appearing before the Subcommittee on Health hearing entitled "Review of the Proposed Generic Drug and Biosimilars User Fees and Further Examination of Drug Shortages" on February 9, 2012.

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for 10 business days to permit Members to submit additional questions to witnesses, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please e-mail your responses, in Word or PDF format, to early.mcwilliams@mail.house.gov by the close of business on Monday, April 2, 2012.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

APR 17 2013

Dear Mr. Chairman:

Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the February 9, 2012, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Review of the Proposed Generic Drug and Biosimilars User Fees and Further Examination of Drug Shortages." This letter provides responses for the record to questions posed by certain Members of the Committee, which we received on March 19, 2012.

Thank you, again, for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

A handwritten signature in cursive script that reads "Michele Mital".

Michele Mital
Acting Associate Commissioner
for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

Page 2 – The Honorable Joseph R. Pitts

We have restated each Member's questions below in bold, followed by our responses.

The Honorable John Shimkus

- 1. As part of the Generic Drug User Fee Act goals, FDA proposes to develop better science for new bioequivalence methods for locally-acting drugs, but does not address the process for developing these methods. Please explain what FDA will do to ensure a transparent process for the development of these methods and utilization of the user fee funds.**

The Generic Drug User Fee Act (GDUFA) program performance goals, which were agreed to by industry representatives, include a regulatory science plan for FY13. The plan includes developing bioequivalence (BE) of local-acting, orally inhaled, topical dermatological and gastrointestinal drug products. In the future, FDA will convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by the Center for Drug Evaluation and Research (CDER) Director.

The Agency intends to fund studies through a granting system or contracts that are open to the public. When the results of these studies become available, they will be published on FDA's publically available website and presented in public venues and, if it is appropriate to base future guidance on the results, these guidance documents will be published in draft form for public comment in accordance with our Good Guidance Practices. The current system for disseminating BE recommendations to the public ensures transparency by allowing an opportunity for interested parties to provide feedback to FDA. The web posting of these draft recommendations is preceded by a *Federal Register* Notice announcing the availability of the newly posted recommendations on FDA's website.

All BE recommendations are posted to the Individual Product Bioequivalence Recommendation page for public comment:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

FDA considers all comments and has revised BE recommendations based on public comments. FDA also discusses complex issues related to BE at the public meetings of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, when appropriate. The results of FDA-funded research projects that support BE method development are generally published in the peer-reviewed scientific literature. These processes ensure transparency, consistency, and scientific rigor of the BE recommendations.

The Honorable Marsha Blackburn

- 1. Do you believe that FDA is doing enough to speed life-saving treatments to seriously ill patients?**

FDA has had a lot of success in expediting the development and approval of lifesaving drugs, particularly drugs for cancer and HIV/AIDS, using existing mechanisms. In fact, a recent *New England Journal of Medicine* article reported that for novel therapeutic agents approved between 2001 and 2010, FDA reviewed applications involving novel therapeutics more quickly, on average, than did the European Medicines Agency (EMA) and Health Canada, and the vast majority of these new therapeutic agents were first approved for use in the United States. For example, among the unique novel therapeutic agents that were approved both by FDA and EMA, 63.7 percent were first approved by FDA.¹ Similarly, the Friends of Cancer Research published a study in *Health Affairs* confirming that new cancer drugs reach patients sooner in the United States than in Europe. The study made a direct drug-to-drug comparison between FDA and EMA approvals of new oncology drugs. The median time for approval for new cancer medicines in the United States was just six months.²

We recognize that we must do more to help expedite drug development and approval in other serious disease settings. FDA has used and continues to use multiple mechanisms to help expedite development and review of important new therapies for serious illnesses. The Accelerated Approval Program and the Fast Track Drug Development Program are examples of these mechanisms, and we continue to consider opportunities to further expand the use of these mechanisms, primarily the accelerated approval mechanism, in other serious disease settings.

2. What are you specifically doing to change the culture at FDA to help these patients?

FDA has a vital role in fostering the application of scientific advances to the treatment of disease through drug development. As such, the culture at FDA is very supportive of looking for new ways to make the drug development system more efficient at developing the evidence necessary to support drug approval, and is actively engaged in those efforts. FDA is developing a series of regulatory policies to further these goals, including drafting guidance on the following: development of two or more novel agents for use in combination, use of adaptive clinical trial designs, non-inferiority clinical trial designs, development of a diagnostic test for use with a drug, use of pathologic complete response as a surrogate endpoint for cancer therapies for use in the neoadjuvant setting (intended to expedite development of new therapies for high-risk, early-stage breast cancer patients), and use of pharmacogenomic analysis in early drug development to better understand variations in clinical response to a drug and to improve the efficiency of subsequent development.

FDA is also engaged in efforts to revise existing guidance, finalized in 1998, on providing clinical evidence of effectiveness to better reflect current clinical and regulatory science and improve the efficiency of drug development. Through efforts such as these, and collaborative efforts such as the recently announced Medical Policy Council, FDA leadership strives to ensure that all FDA staff fully embrace these forward-looking and innovative processes and ideas.

¹“Regulatory Review of Novel Therapeutics—Comparison of Three Regulatory Agencies,” Nicholas S. Downing, A.B, et al., *New England Journal of Medicine*, 366:24, June 24, 2012.

²“Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe,” Samantha A. Roberts, Jeff D. Allen, and Ellen V. Sigal, *Health Affairs*, June 2011.

3. Why has the current FDA seemingly rejected the accelerated approval regulations that the Agency had been following for over a decade?

Accelerated Approval is a vital and increasingly important mechanism for providing patients with serious and life-threatening conditions access to promising new therapies as soon as possible and, as noted above, is seeking to expand its use. For example, in an effort to foster development of new therapies for breast cancer, FDA published a draft guidance in May 2012 recommending use of a new surrogate endpoint (an endpoint that has not been previously used as a surrogate in this disease setting) to support accelerated approval of drugs for use in early-stage breast cancer (see Guidance for Industry, “Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval,” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf>).

Over 80 new products have been approved under Accelerated Approval since the program was established, including 29 new drugs to treat cancer, 32 to treat HIV, and 20 to treat other conditions, such as pulmonary hypertension, Fabry disease, and transfusion-dependent anemia. Since 1995, there have been 49 new indications for 37 oncology products using Accelerated Approval.

4. Do you believe the 1992 accelerated approval regulations and regulatory approach to fast-track approval adopted by the Clinton Administration was not in the best interest of patients?

On the contrary, these regulations are in the best interest of patients, because these programs strike the right balance between providing patients with timely access to important FDA-approved new drugs and protecting patients from being exposed to drugs that are not safe or effective. FDA administers a number of existing programs to expedite the approval of certain promising investigational drugs, and also to make them available to the very ill before they have been approved for marketing, without unduly jeopardizing patient safety, including Accelerated Approval and Fast Track.

In 1992, FDA instituted the Accelerated Approval process, which allows earlier approval of drugs that treat serious or life-threatening diseases and that provide meaningful therapeutic benefit over existing treatments based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not fully validated to do so, or, in some cases, an effect on a clinical endpoint other than survival or irreversible morbidity. A surrogate endpoint is a marker—a laboratory measurement, or physical sign—that is used in clinical trials as an indirect or substitute measurement for a clinically meaningful outcome, such as survival or symptom improvement. For example, viral load is a surrogate endpoint for approval of drugs for the treatment of HIV/AIDS. The use of a surrogate endpoint can considerably shorten the time to approval, allowing more rapid patient access to promising new treatments for serious or life-threatening diseases. Accelerated Approval is given on the condition that sponsors conduct post-marketing clinical trials to verify the anticipated clinical benefit. The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, P.L. 112-144, codifies in law and

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clarifies the Accelerated Approval pathway, including listing the types of evidence upon which FDA can rely when determining whether a surrogate or clinical endpoint is valid.

Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases that will fill an unmet medical need. Once a drug receives Fast-Track designation, early and frequent communications between FDA and a drug company are encouraged throughout the entire drug development and review process. The frequency of communications ensures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients. For example, Zelboraf (vemurafenib) was given a Fast-Track designation because it had the potential to improve overall survival in patients with melanoma, the most dangerous type of skin cancer. Because of convincing early findings with this drug, FDA scientists worked proactively with the sponsor during drug testing to encourage early submission of the application. FDA approved Zelboraf in 2011 to treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma.

5. **Do you agree that additional legislative authority is needed to address FDA's reluctance to utilize the fast-track authority first adopted over a decade ago, or to provide the FDA with additional flexibility or incentive to approve drugs for serious and life-threatening illnesses?**

As noted in response to questions 3 and 4, we remain committed to using existing programs, such as Accelerated Approval and Fast Track, to speed therapies to patients while protecting patients from being exposed to therapies that are not safe or effective. Balancing these two objectives requires that we continue to evaluate our use of the tools available to us and consider whether additional tools would be helpful. Section 902 of FDASIA establishes a new pathway for breakthrough therapies, which are defined as drugs that are intended to treat a serious or life-threatening disease or condition and for which preliminary clinical evidence demonstrates substantial improvement over existing therapies. Drugs that receive this designation are eligible for additional consultation with the Agency to design an expedited drug development pathway.

The Honorable Tim Murphy

1. **What is the current level of Agency prioritization for biosimilars? How many reviewers has the Agency trained on review of biosimilars? How many reviewers does the Agency believe are needed to review biosimilars? Will the same reviewers also review the originator products? What does the Agency plan on doing to make sure that there is no conflict of interest? Has the Agency thought about creating a separate dedicated office for biosimilars? If no, why not?**

FDA considers the review of biosimilar biological products—which offer the potential for a safe and effective and more affordable alternative to innovator biologics—to be a high priority. Following the March 23, 2010, enactment of the Biologics Price Competition and Innovation Act (BPCIA) as part of the Patient Protection and Affordable Care Act, P.L. 111-148, FDA began developing regulatory policies and guidance on the new biosimilar approval pathway and training reviewers in an effort to help build review capacity and ensure consistent advice to

sponsors concerning biosimilars biological product development. Because an approval pathway for biosimilar biological products was established only three years ago, the volume of submissions in connection with biosimilar biological product development is still small. Nonetheless, FDA has devoted an increasing amount of resources to biosimilars since March 2010. By September 2010, FDA was devoting the equivalent of 15 Full Time Equivalents (FTEs) to biosimilars work that included a significant amount of policy development to implement the program. In May 2010, FDA began meeting with sponsors of biosimilar applications. This activity increased and by the spring of 2011, FDA had devoted 26 FTEs to biosimilars work. The biosimilars industry and regulatory program are relatively new, leading to uncertainty regarding future program size. Under the Biosimilar User Fee Act (BsUFA), enacted on July 9, 2012, as part of FDASIA, FDA would allocate at least the inflation adjusted value of \$20 million in non-user-fee money for biosimilar review activities, plus biosimilar user fee collections.

Characterizing biological products for the purpose of determining biosimilarity or interchangeability differs from work with small-molecule drugs because the molecules of biological products tend to be much larger and have a far more complex spatial structure than small-molecule drugs. To ensure the highest level of clinical and technical expertise in biosimilar review, and the greatest efficiency and consistency in review program operations, FDA does not plan to create a separate office for biosimilars review. Familiarity with the innovator product will be important in conducting an efficient and informed assessment of the biosimilar product. FDA also notes that the Public Health Service Act (PHS Act), as amended by the BPCIA, requires that an application for a proposed biosimilar or interchangeable product be reviewed by the division within FDA that is responsible for the review and approval of the application under which the reference product is licensed (see section 351(k)(5)(B) of the PHS Act).

FDA does not consider additional steps, beyond the extensive conflict-of-interest screening and management that apply to all regulated product reviews, to be necessary for biosimilar biologics. BsUFA will further ensure that distinct and adequate resources are available to support rapid review of both 351(k) applications and 351(a) applications.

2. What is the internal process for biosimilar applicant meetings? Is it accurate that the FDA has had four internal meetings before every meeting with sponsors for PreIND meetings? Does the FDA plan to keep the number of meetings flexible and not mandatory?

It is FDA's long-standing practice to conduct internal meetings prior to meeting with sponsors to discuss the submitted content and to develop responses to the sponsor's questions. For the biosimilar development program proposals, CDER has, in practice, found that, based on the complexity of the proposals and the breadth of the advice sought, several internal meetings, including the internal Biosimilar Review Committee meeting, are typically necessary to adequately discuss the scientific and policy issues and to develop meaningful and consistent advice to sponsors. The number of internal meetings is not mandatory and is flexible based on the scope of the meeting and the stage of product development.

3. Is it accurate that the FDA is proposing 4 pre-filing meetings (Types 1 through 4)? Does this mean that a 351(k) applicant will be prohibited from meeting with the Agency after they have had 4 pre-filing meetings?

FDA proposed five meeting types consisting of a Biosimilar Initial Advisory Meeting, and Biosimilar Biological Product Development (BPD) Meeting Types 1 through 4. These meetings are not mandatory. Sponsors can choose the meeting or the combination of meetings to match their development needs, and there is no limit on the number of BPD meetings. FDA will grant a meeting request if the Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). Requests for BPD Type 2, 3 and 4 meetings will be honored, except in the most unusual circumstances.

4. What is the average waiting period for sponsors following a request for a meeting under PDUFA versus a meeting to discuss a biosimilar application?

As agreed to with industry, the proposed performance goals for BsUFA include goals related to meetings with sponsors on biosimilar biological product applications. These goals are similar in structure to the current PDUFA meeting goals in that they include commitments for scheduling meetings within target time frames that depend on the type of meeting requested. The proposed BsUFA performance goals for scheduling meetings within the target time frames start at the 70 percent performance level in the first year of the program and increase to the 90 percent performance level in the fifth year of the program. The current PDUFA performance goals for scheduling meetings are set at the 90 percent performance level. A comparison of the target time frames for the different PDUFA and BsUFA meeting types is provided below:

Meeting Goals (in calendar days)	PDUFA Type A Meeting	PDUFA Type B Meeting	PDUFA Type C Meeting	BsUFA Initial Advisory Meeting	BsUFA BPD 1 Meeting	BsUFA BPD 2 Meeting	BsUFA BPD 3 Meeting	BsUFA BPD 4 Meeting
Meeting Requests	14 days	21 days	21 days	21 days	14 days	21 days	21 days	21 days
Scheduling Meetings	30 days	60 days	75 days	90 days	30 days	75 days	120 days	60 days
Meeting Minutes	30 days	30 days	30 days	30 days	30 days	30 days	30 days	30 days

The Biosimilar Initial Advisory Meeting is an initial assessment limited to a general discussion regarding whether the biosimilar licensure pathway may be feasible for a particular product, and, if so, general advice on the expected content of the development program. Such meetings will typically involve the review of a comprehensive development proposal. There is no meeting type that is comparable to a Biosimilar Initial Advisory Meeting under PDUFA. The Type A meeting under PDUFA and BPD Type 1 meeting under BsUFA are identical in intent. These meetings have short target time frames because they are held to discuss at risk clinical development programs and other imminent issues. The BPD Type 2 meeting under BsUFA is similar in intent to a Type B meeting under PDUFA and will involve the review of study summaries and discussion of milestones in product development. The BPD Type 3 meeting will involve the review of full-study reports, rather than summaries, which necessitates an in-depth data review. FDA will provide advice regarding the similarity between the proposed biosimilar

biological product and the reference product, and advice regarding additional studies, including design and analysis. This type of review and assessment requires more preparation time by the Agency than for other meeting types. There is no meeting type under PDUFA that is comparable to a BPD Type 3 meeting. The BPD Type 4 meeting under BsUFA is identical in intent and content to a certain kind of Type B meeting under PDUFA, where the content and format of a planned NDA or BLA application is discussed. There is no meeting type under BsUFA that is comparable to the Type C meeting under PDUFA, which serves as a general meeting category to include meetings that are not considered Type A or B.

With the combined resources of at least the inflation-adjusted value of \$20 million in non-user-fee funds, plus biosimilar-user-fee collections, FDA expects to be able to achieve these meeting performance goals in the first five years of the BsUFA program.

5. What is FDA’s rationale for requesting an upfront fee from biosimilar applicants under BsUFA and not from sponsors of BLAs under PDUFA?

Because of the nascent state of the biosimilars industry in the United States, there are no currently marketed biosimilar biological products. Accordingly, BsUFA, as agreed to by industry, includes fees for products in the development phase (“biosimilar biological product development fees”) to generate fee revenue in the near-term and ensure that FDA has the increased review staff capacity to enable sponsors to have timely meetings with FDA early in and throughout the development of biosimilar biological product candidates. Under the proposed program, the application fee amount for a biosimilar biological product is set equal to the application fee amount established under PDUFA for that fiscal year. However, when a biological product application is submitted, the cumulative amount of any biosimilar biological product development fees paid for that product is subtracted from the amount of the application fee that otherwise would be due.

6. FDA granted interchangeability to a very complex glycosylated molecule. Although not a biologic, the Enoxaparin approval demonstrates the FDA’s level of comfort with state-of-the-art characterization technology as an appropriate basis to grant interchangeability between a generic and the reference product. Isn’t this the same standard that will be used for biosimilar products irrespective of interchangeability? If so, why does the Agency not believe that interchangeability is possible today?

As a preliminary matter, we note that the term “interchangeability” is defined by statute to refer to a biological product shown to meet the standards described in section 351(k)(4) of the PHS Act and this statutory definition does not apply to a drug product, such as enoxaparin, that has been approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA has approved abbreviated new drug applications (ANDAs) for enoxaparin under section 505(j) of the FD&C Act, based on the applicant’s submission of sufficient information to show that its proposed product is bioequivalent to and has the “same” active ingredient, route of administration, dosage form, strength, previously approved conditions of use, and (with certain exceptions) labeling as the reference listed drug (RLD). The underlying premise of the ANDA

approval requirements is that the generic drug product and the RLD can be substituted for each other with the full expectation that they will have the same clinical effect and safety profile.

FDA scientists established a scientific approach for demonstrating active ingredient sameness that takes into consideration the complexity of enoxaparin. This scientific approach is reflected in five criteria, which involve: (1) the physical and chemical characteristics of enoxaparin; (2) the nature of the heparin material and the chemical process used to break up heparin chains into smaller pieces; (3) the nature and arrangement of components that constitute enoxaparin; (4) certain laboratory measurements of the product's anticoagulant activity; and (5) certain aspects of the drug's effect in humans. These five criteria ensure that a generic enoxaparin drug product will have the same active ingredient as the brand-name product. This requirement, together with other requirements for ANDA approval, will ensure that the generic enoxaparin drug product will have the same effects as the brand-name drug product when injected into a patient. (By contrast, a biological product proposed in a 351(k) application must show, among other things, that the biological product is "highly similar" to the reference product, notwithstanding minor differences in clinically inactive components.)

Protein products differ from enoxaparin in important ways. Enoxaparin is a complex carbohydrate that lacks the types of 3-dimensional structural characteristics found in proteins. Enoxaparin is also relatively stable and is produced via a specific chemical cleavage of heparin. In contrast, proteins are relatively labile molecules and can be manufactured in a variety of ways that can impact structural features. Thus different scientific expectations are appropriate for proteins.

If a sponsor is interested in developing a biological product that meets the requirements for interchangeability as described under 351(k)(4) of the PHS Act, the Agency is interested in discussing such a development plan with the sponsor.

7. Does the Agency believe the current law prohibits a biosimilar product from automatically being deemed interchangeable?

To receive a determination of "interchangeability," the applicant needs to provide information sufficient to show that the proposed product meets the requirements in section 351(k)(4) of the PHS Act.

8. If a 351(k) applicant is seeking an interchangeable determination, but plans on marketing the product after a biosimilar determination, do they have to submit a pediatric study plan? If so, when?

Section 505B(n) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of the Pediatric Research Equity Act (PREA), and a pediatric assessment is required unless waived or deferred. FDA encourages prospective biosimilar applicants to discuss their proposed approach to addressing this requirement, or requesting a waiver or deferral if appropriate, during the investigational new drug (IND) stage of product development.

9. **Although use of a foreign reference product is allowed in a biogeneric development program, the regulatory burden of utilizing a foreign comparator is considerably higher, and use of a foreign reference product is effectively precluded for an interchangeable biogeneric. Can you expand on the biosimilars guidance regarding this from a scientific standpoint?**

Section 351(i)(4) of the PHS Act, as amended by the BPCIA, defines the “reference product” for a proposed biosimilar product to mean the single biological product licensed under section 351(a) of the PHS Act, against which a biological product is evaluated in a 351(k) application. Accordingly, a non-U.S.-licensed product cannot be a “reference product.”

A sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. We note, however, that for certain complex biological products, a modified approach may be needed.

If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed likely would include a clinical PK and/or PD study conducted with the U.S.-licensed reference product.

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include, but are not limited to, the following:

- the relevance of the design of the clinical program to support a demonstration of biosimilarity to the U.S.-licensed reference product for the condition(s) of use and patient population(s) for which licensure is sought;
- the relationship between the license holder for the non-U.S.-licensed product and BLA holder for the U.S.-licensed reference product, including whether the non-U.S.-licensed product, and/or any components thereof, are manufactured in the same facility(ies) as the U.S.-licensed reference product during the relevant time period;
- whether the non-U.S.-licensed product was manufactured in a facility(ies) licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries);
- whether the non-U.S.-licensed product was licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., ICH countries) and the duration and extent to which the product has been marketed; and
- the scientific bridge between the non-U.S.-licensed product and the U.S.-licensed reference product, including comparative physico-chemical characterization,

bioassays/functional assays, and comparative clinical and/or nonclinical PK and/or PD data, as appropriate, and data to address any differences in formulation or primary packaging.

A sponsor also should address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by FDA during review of the 351(k) application.

At this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.

- 10. Do you agree with the statement that there is intrinsic variation seen in biologic products today for the originator's products and that their sponsors provide assurances as to the limits of the variation that is allowed to the FDA to evaluate post-approval changes in originator biologic products? And would you agree that this has been the case for well over 15 years to determine that the revised originator product (due to the Originator making a manufacturing or process changes after market entry) is interchangeable with the original approved originator biologic?**

The observation that some structural differences may be found in biological products over time is not unexpected. Such differences are most often associated with manufacturing changes intended to improve the process. Under FDA regulations, manufacturers of licensed biological products are required to report to FDA all post-approval manufacturing or process changes (post-approval changes).³ In some cases, manufacturers must also seek prior approval before implementing a particular post-approval change. As part of the reporting requirement, license holders are also required to assess the effect of any post-approval change on the identity, strength, quality, purity, and potency of a licensed biological product as it may relate to the safety or efficacy of the product (comparability assessment).

Manufacturers report post-approval changes under one of several reporting categories described in Agency regulations, based on the results of the comparability assessment. Before distributing a product manufactured after a post-approval change, license holders are required to demonstrate, through appropriate validation and/or other clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as it may relate to the safety or effectiveness of the product.

³ 21 CFR § 601.12

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For major manufacturing changes that have a substantial potential to impact the safety and/or effectiveness of the product, data supporting the changes are submitted to the Agency in a prior approval supplement for review and approval. If structural differences and/or the nature of the manufacturing change are of concern to FDA, appropriate additional studies, including analytical, biological, non-clinical and clinical studies, are requested and evaluated by the Agency.

It should be noted that although different pre- and post-change versions of originator products may overlap on the market for a short period of time, the newer version generally becomes the only marketed version after that time and repeated switches between pre- and post-change versions are less likely.

11. **Then, given that the science is the science, shouldn't that same standard apply for interchangeable bigeneric products? If the bigeneric manufacturer can demonstrate that its product falls within the limits of the variation shown by the originator product and that the product is comparable in all other respects and can be expected to produce the same clinical result, then shouldn't the FDA deem it interchangeable?**

Under section 351(k)(4) of the PHS Act, as added by the BPCIA, FDA shall determine the biological product to be "interchangeable" with the reference product if the information submitted in the 351(k) application (or supplement to such application) is sufficient to show that the product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient. If the biological product is administered more than once to an individual, the information in the application must also show that the risk, in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product, is not greater than the risk of using the reference product without such alternation or switch.

The Honorable Leonard Lance

1. **In GDUFA FDA proposes to develop better science for new bioequivalence methods for locally- acting drugs, but does not address the process for developing these methods. Bioequivalence is key to ensuring that generic drugs are the same. But the level of evidence, process, and transparency for these methods has varied greatly. What will FDA do differently to ensure a transparent, open process going forward, and what can be done about current methods that have lacked transparency to ensure that these methods are scientifically sound and protect the public health now and in the future?**

The GDUFA Program performance goals, which were agreed to by industry representatives, include a regulatory science plan for FY13. The plan includes developing BE of local-acting, orally inhaled, topical dermatological and gastrointestinal drug products. In the future, FDA will convene a working group and consider suggestions from industry and other stakeholders to

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develop an annual list of regulatory science initiatives for review by the Center for Drug Evaluation and Research (CDER) Director.

The Agency intends to utilize generic drug user fee funds to fund studies through a granting system or contracts that are open to the public. When the results of these studies become available, they will be published on FDA's publically available website and presented in public venues and, if it is appropriate to base future guidance on the results, these guidance documents will be published in draft form for public comment in accordance with our Good Guidance Practices. The current system for disseminating BE recommendations to the public ensures transparency by allowing an opportunity for interested parties to provide feedback to FDA. The web posting of these draft recommendations is preceded by a *Federal Register* Notice announcing the availability of the newly posted recommendations on the FDA's website.

All BE recommendations are posted to the Individual Product Bioequivalence Recommendation page for public comment:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

FDA considers all comments and has changed BE recommendations based on public comments. FDA also discusses complex issues related to BE at the public meetings of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, when appropriate. The results of FDA-funded research projects that support BE method development are generally published in the peer-reviewed scientific literature. These processes ensure transparency, consistency, and scientific rigor of the BE recommendations.

2. **The public expects that a generic drug will work the same as the brand drug. Yet, in some of your speeches you have highlighted quality issues with generic drugs. Generic drugs are a critically important component of our health care system and helps control costs but how can I assure my constituents that generic drugs are the same as the brand products when the data relied on, and the rationale are not publicly discussed especially in dosage forms where the bioequivalence methods are not straight forward such as locally-acting drugs?**

FDA approves a generic drug only after it has determined that it is the same as a brand-name drug in dosage, safety, strength, quality, the way it works, the way it is taken and the way it should be used. In her testimony before this Committee in support of generic drug user fees, Dr. Woodcock did note the "regulatory challenge of ensuring safe, high-quality generic drugs includes inspecting manufacturing facilities, where the challenge is not just one of numbers but also of geography. To keep pace with the growth of the Generic drug industry, FDA has had to conduct more inspections as the number of facilities supporting those applications has also increased, with the greatest increase coming from foreign facilities." With enactment of the Food and Drug Administration Safety and Innovation Act, P.L. 112-144, which includes a provision for generic drug user fees, FDA expects the backlog of generic drug applications to be reduced, and for generic drugs to get to market faster.

Regarding the issue of bioequivalence, as stated above, all BE recommendations are posted to the Individual Product Bioequivalence Recommendation page for public comment: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>. FDA considers all comments and has changed BE recommendations based on public comments. FDA also discusses complex issues related to BE at the public meetings of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, when appropriate. The results of FDA-funded research projects that support BE method development are generally published in the peer-reviewed scientific literature. These processes ensure transparency, consistency, and scientific rigor of the BE recommendations

3. **Please have your staff follow up with the Committee's staff on some specific questions about certain bioequivalence methods that FDA's Office of Generic Drugs has proposed.**

FDA's Office of Legislation has contacted your staff to further discuss your Committee's specific questions about BE methods.

4. **Has FDA's pharmacokinetic bioequivalence method for generic lidocaine patches been validated with data showing it is sensitive enough both to weed out generic products that risk inadvertent trauma by blocking sensation in the skin, and also detect whether generics deliver enough active ingredient to achieve pain relief? I am concerned that if not, patients accustomed to the brand product's analgesia without complete sensory block may injure themselves, or continue to experience pain. For the first topical patch used to treat a skin disorder where FDA (or at least the Office of Generic Drugs) has decided that clinical bioequivalence studies are not needed, I am concerned FDA has not made public or discussed the data it relied on for this significant change in standards of generic sameness.**

The Agency addressed these issues in responding to a Citizen Petition on August 22, 2012. Our response letter is available in docket number FDA-2006-P-0346, available at <http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0346-0017>.

5. **Has FDA reassessed the efficacy of generic antibiotics in light of last year's study by Vesga et al., showing "Generic Vancomycin Products Fail In Vivo despite Being Pharmaceutical Equivalents of the Innovator"? Is FDA certain, despite this work showing FDA's standard tests for generic equivalence failed to detect ineffective generic versions of this life-saving antibiotic sold overseas, that vancomycin generics in the US actually work as well as the brand? Can you assure me that FDA will not approve generic vancomycin capsule products without an in vivo demonstration of efficacy or at least an in vitro test that has been correlated with in vivo data in actual patients?**

These issues were the subject of a Citizen Petition filed by ViroPharma, Inc., the sponsor of the innovator products. The Agency issued a response to this petition on April 9, 2012. As addressed in detail in the citizen petition response, the Vesga articles, which concern injectable vancomycin and not the capsule solid oral dosage form, provided no basis in support of the position

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that either generic vancomycin injectable products or capsules approved by FDA are less effective than the innovator product Vancocin. ViroPharma filed a lawsuit challenging FDA's response on April 13, 2012, but did not challenge the agency's conclusions with respect to the Vesga articles. On January 9, 2013, the Court granted FDA summary judgment, and ViroPharma did not appeal the court's decision. We would be happy to provide a copy of the petition response to your office, and the response is available publicly on www.regulations.gov.

6. **For each of these examples, did the NIH, NSF, NIST or other outside experts assess the data on which FDA relies and agree they are sufficient to ensure FDA's proposed bioequivalence methods for these products will only allow approval of generics that produce identical results in patients? Have these assessments of data sufficiency for these bioequivalence methods been made available for public review? If not, why not? Can you assure me that FDA will not expose American patients to unproven generic versions of these drugs until these steps have been taken?**

FDA's process for obtaining external scientific input is through the Advisory Committee process (which could involve experts from these and other organizations) and through public comments submitted to the individual product recommendation docket. FDA has no current plans for assessments of BE methods outside of the public advisory committee processes.

*Subcommittee on Health hearing entitled "Review of the Proposed Generic Drug and
Biosimilars User Fees and Further Examination of Drug Shortages
April 2, 2012
Additional Questions for the Record*

Responses of Heather Bresch

The Honorable Marsha Blackburn

1. We are hearing from our community pharmacies in Tennessee, and overwhelmingly – in fact 96% of them – they are experiencing shortages in the past 6 months.

a. What are you currently doing about the massive shortages experienced outside of hospitals – in chemical drugs, in our communities and especially for patients in need of ADHD drugs?

Mylan does not currently manufacture the oral solid and transdermal drugs presently listed on the FDA's drug shortage list, including ADHD drugs. However, we continue to work closely with the FDA in an attempt to address drug shortages in areas where we are in a position to help provide relief. These include injectables in short supply due to manufacturing issues at other suppliers, such as preservative-free Methotrexate Injection for the treatment of patients with cancer, particularly the pediatric population. In that instance, Mylan's subsidiary, Mylan Institutional, has ramped up production and reallocated resources in order to try to address the reduced supply and enable the manufacture of as much preservative-free Methotrexate Injection as possible. Mylan Institutional is also aggressively working on both the manufacturing and regulatory fronts in an effort to help expedite the FDA regulatory approvals necessary to further increase capacity.

b. What ideas can help alleviate these concerns?

The issues associated with drug shortages and how to solve them are complex and varied, and multiple stakeholders have a part to play in addressing them, including manufacturers, active pharmaceutical ingredient (API) suppliers, FDA, group purchasing organizations (GPOs), distributors, wholesalers, retailers, and end-users.

It is also our view that prevention is extremely important. That is why we believe the historic Generic Drug User Fee Act (GDUFA), which is focused on securing the integrity of the global supply chain by ensuring that all participants in the U.S. drug system – domestic and foreign –

comply with U.S. quality standards, and decreasing the FDA's average review times, which will expedite the availability to consumers of low cost, high quality generic drugs, will play a key part in addressing drug shortages going forward. For example, shortages are sometimes linked to a problem in the manufacturing process that could possibly have been addressed through the inspection process. In addition, accelerating the market entry of new manufacturers of drugs currently in short supply and improving quality, consistency and availability within the supply chain, also will help to mitigate drug shortages caused by interrupted access to raw materials, such as active pharmaceutical ingredients.

Additionally, the Generic Pharmaceutical Association (GPhA) is developing a multi-stakeholder tool, known as the Accelerated Recovery Initiative (ARI), with the intent of accelerating the recovery of certain critical drugs in short supply.

We are also supportive of the Expedited Review and Quota sections of the Energy and Commerce Committee's recently released discussion draft document and believe that, if passed by Congress, this particular language would also help industry and FDA better respond to drug shortages.

c. Should the DEA ease its rules on production of this class of drugs to allow larger lots to be produced?

As we all work to address drug shortages, it is important that the FDA and DEA are coordinating closely, so that flexibility with regard to quotas can be granted if needed. It is for this reason that we are supportive of the Quota section of the Energy and Commerce Committee's recently released discussion draft document.



Mr. David Gaugh, Vice President Regulatory Affairs
Response to Questions for the Record
February 9, 2012
Energy and Commerce Subcommittee on Health
“Review of the Proposed Generic Drug and Biosimilars User Fees and Further Examination of Drug Shortages”

The Honorable Marsha Blackburn

We are hearing from our community pharmacies in Tennessee, and overwhelmingly-in fact 96% of them-they are experiencing shortages in the last 6 months.

- a. What are you currently doing about the massive shortages experiences outside of hospitals-in chemical drugs, in our communities and especially for patients in need of ADHD drugs?
- b. What ideas can help alleviate these concerns?

GPhA and our members take the health and safety of patients very seriously. We are proud of our record of expanding access to high quality, affordable medications to all Americans.

Drug shortages result from a variety of reasons. Causal factors of drug shortages, rather, are numerous and do not apply in every case. They include everything from an insufficient supply of available raw materials, to increasing consumer demand, to decreasing available capacity due to quality and/or compliance issues, to inadequate and delayed communications about shortages. For example, raw materials used to manufacture certain drugs can suddenly be in short supply, and consumer demand can increase. Moreover, in certain situations, manufacturers have had to temporarily halt production due to suspected quality concerns with raw materials or manufacturing processes. In our view, safety of supply is paramount. . Finally, perceived shortages, or reports of shortages, can result in medication stockpiling, unintentionally exacerbating drug shortages in the system.

In regards to drug shortages, specifically shortages of ADHD drugs, GPhA feels that the issue is best handled by FDA and DEA. The two agencies have agreed to work together to address this specific situation. FDA's Valerie Jensen said "FDA is doing everything within its regulatory authority to address these shortages when they occur."¹ GPhA continues to work with both the FDA and DEA to find solutions that address the core issues causing drug shortages. All prescriptions, including ADHD drugs, are vital to consumers who rely on them every day. Our members are attempting to meet the market demand while working closely with the agencies to ensure proper patient access.

GPhA hopes the agencies work together to create an appropriate regulatory environment to address the concerns of patients, Congress, and manufacturers.

- c. Should the DEA ease its rules on production of this class of drugs to allow larger lots to be produced?

GPhA believes that decisions on matters such as these, which are largely regulatory and/or science based, should be made by the FDA and the drug company that produces ADHD drugs.

¹ FDA Website, "FDA Works to Lessen Drug Shortage Impact."
<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm258152.htm>

Responses for the Record
 Health Subcommittee of the House Energy & Commerce Committee
 February 9, 2012; Responses provide March 26, 2012
 William Greene, PharmD, BCPS, FASHP

Responses to Questions Offered by Congressman Blackburn

1) **We are hearing from our community pharmacies in Tennessee, and overwhelmingly – in fact 96% of them – they are experiencing shortages in the past 6 months.**

a) **What are you currently doing about the massive shortages experienced outside of hospitals - in chemical drugs, in our communities and especially for patients in need of ADHD drugs?**

Response:

Drug shortages are impacting pharmacies in all practice settings. At St Jude, we provide medications to inpatients and to outpatients. The shortages experienced by community pharmacists are also impacting St Jude. We handle these shortages in much the same way as other pharmacies: we pursue supplies through our various wholesaler relationships, we exert extra personnel time to the effort of inventory control and being sure that we identify and secure drug supplies, we collaborate with other health care providers in order to define alternative therapy when needed, and we educate families and prescribers regarding all the different challenges presented by drug shortages. We do have a policy of strictly avoiding products which are offered through the so-called "Gray Market," because of the inability to be sure of the integrity of drugs purchased through these avenues and because we do not want to contribute to the efforts of unscrupulous vendors.

b) **What ideas can help alleviate these concerns?**

Response:

As suggested during my testimony, there are several steps that would be helpful today:

- give the FDA tools that it needs to prevent and minimize the impact of drug shortages including manufacturer notification to the FDA when a company is leaving the market or curtailing production, and mandatory notification to the FDA of conditions that could result in drug shortages
- give the FDA adequate resources to be able to develop relevant databases and forecasting approaches
- give providers notice of upcoming shortages to mitigate patient impact as much as possible
- engage pediatric practitioners in crafting any proposed solutions
- before enacting legislation directed at correcting underlying factors contributing to shortages, be very careful to fully understand the implications and impact of the legislative action

c) **Should the DEA ease its rules on production of this class of drugs to allow larger lots to be produced?**

Response:

It is generally perceived that the inflexibility of the DEA has contributed to difficulties in manufacturers' ability to modify production in response to production changes by other manufacturers. If this is the case, DEA should work more collaboratively with the FDA in developing appropriate plans to address real or pending drug shortages.

Responses to Questions Offered by Congressman Pallone

1) **Dr. Greene, an exchange during the hearing, between you and Dr. Cassidy (R-LA) seemed to confuse the issue of whether the 340B Drug Discount Program contributed to a recent IVIG shortage. Dr. Cassidy suggested during the exchange that IVIG's removal from the 340B alleviated the shortage.**

a) However, isn't it true that IVIG remains 340B eligible today and, in fact, has never been removed from the 340B program?

Response:

I have practiced pharmacy for more than 30 years, and have served as a pharmacy leader in two different health care organizations since 1991. Although St Jude has participated in the 340B Discount Program only since January 2010, I had some experience with the program at the institution where I was formerly employed through 2007. Based on my experience and on information from colleagues and pharmacy professional groups, it is my understanding that IVIG has never been granted an exemption from the 340B program or removed from the program, and it remains available at 340B prices today.

b) Furthermore, and separate from any specific issues with IVIG supply, isn't it also true that there is little evidence linking the longstanding 340B program to the recent upswing in drug shortages?

Response:

This is true. I am aware of no evidence that links the increase in drug shortages to the 340B program.