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FDA USER FEES 2012: ISSUES RELATED TO ACCELERATED APPROVAL, MEDICAL GAS, ANTIBIOTIC DEVELOPMENT, AND DOWNSTREAM PHARMACEUTICAL SUPPLY CHAIN

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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FDA USER FEES 2012: ISSUES RELATED TO ACCELERATED APPROVAL, MEDICAL GAS, ANTIBIOTIC DEVELOPMENT, AND DOWNSTREAM PHARMACEUTICAL SUPPLY CHAIN

THURSDAY, MARCH 8, 2012

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

The subcommittee met, pursuant to call, at 10:16 a.m., in room 2322 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, Townes, Schakowsky, and Waxman (ex officio).

Staff present: Clay Alspach, Counsel, Health; Andy Duberstein, Deputy Press Secretary; Nancy Dunlap, Health Fellow; Paul Edattel, Professional Staff Member, Health; Debbee Keller, Press Secretary; Ryan Long, Chief Counsel, Health; Carly McWilliams, Legislative Clerk; Chris Sarley, Policy Coordinator, Environment and Economy; Brett Scott, Staff Assistant; Heidi Stirrup, Health Policy Coordinator; Alli Corr, Democratic Policy Analyst; Eric Flamm, FDA Detailee; Karen Lightfoot, Democratic Communications Director and Senior Policy Advisor; Karen Nelson, Democratic Deputy Committee Staff Director for Health; and Rachel Sher, Democratic Senior Counsel.

Mr. PITTS. This subcommittee will come to order.

The Chair recognizes himself for 5 minutes for an opening statement.

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

Today we are taking a more in-depth look at several issues related to the FDA user fee programs. First, we will hear about FDA's Accelerated Approval process for certain new drugs that treat serious or life-threatening illnesses and provide a greater therapeutic benefit over existing drugs and therapies. Accelerated Approval has been successful in speeding cancer and HIV/AIDS drugs to market, and I am particularly interested in how the process can be better utilized for rare diseases.

Earlier this week, Representative Stearns, along with Representatives Bilbray and Towns, introduced the Faster Access to Special-

ized Treatments, the FAST Act, to help expedite new drugs through the approval process.

We will also hear about FDA's regulation of medical gas and the need for targeted regulations for these substances, due to their differences from most drugs.

Representative Lance has introduced H.R. 2227, the Medical Gas Safety Act, which would reform the current FDA regulation of medical gases to create an appropriate process for medical gases to be approved. It would also remove the current regulatory uncertainty for medical gases by establishing targeted regulations that take into account the unique characteristics of medical gases. Representative Lance's bill is bipartisan. It is cosponsored by members of the full committee from both sides of the aisle.

Next, we will address the lack of new antibiotics in the pipeline and how Congress and FDA can act to incentivize new antibiotic development.

Dr. Gingrey's Generating Antibiotic Incentives Now Act, or the GAIN Act, H.R. 2182, targets this problem. This bill would extend the exclusivity period for new prescription antibiotics and add an additional 6-month period of exclusivity for a manufacturer if the new antibiotic identifies a companion diagnostic test. The GAIN Act also has bipartisan support, including eight Democrats and 15 Republicans from the full committee.

Finally, the subcommittee will hear about the dangers and weaknesses to the current pharmaceutical supply chain from manufacturers, to distributors, to pharmacies, and how best to ensure that counterfeit, adulterated or stolen drugs do not end up in the hands of patients.

Representative Bilbray and Representative Matheson are currently working in this area, and Dr. Cassidy's Online Pharmacy Safety Act, H.R. 4095, aims to educate the public about which Internet pharmacies are known to be safe and legitimate.

We have three panels today. I would like to thank all of our witnesses for being here. I look forward to their testimony.

[The prepared statement of Mr. Pitts follows:]

Opening Statement of the Honorable Joseph R. Pitts
Subcommittee on Health
Hearing on "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain"
March 8, 2012
(As prepared for delivery)

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I would like to thank our witnesses for being here, and I look forward to your testimony.

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Mr. PITTS. So at this time I recognize the ranking member of the Subcommittee on Health, Mr. Pallone, for 1 minute—oh, 5 minutes. I am sorry.

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

Mr. PALLONE. Thank you, Chairman Pitts.

Today we are holding another hearing to examine important FDA-related issues that could be considered as a part of the user fee agreements, or the UFA legislation. These include changes to the current expedited approval process for new drugs, the regulation of medical gases, antibiotic drug development, and the downstream pharmaceutical supply chain. It is my hope that our witnesses that will help the subcommittee examine the ways in which these issues can be or should be addressed in our upcoming legislation.

Accelerated Approval is one of the processes by which the FDA approves certain New Drug Applications that offer meaningful therapeutic benefit over existing treatments for serious or life-threatening diseases. This process has been responsible for the great strides in medicine to treat HIV and cancer, and has provided patients with speedier access to important new medicines.

According to the FDA, over 80 new products have been approved under Accelerated Approval since the program was established including 29 drugs to treat cancer, 32 to treat HIV, and 20 to treat various other conditions. There are also two other programs that help expedite the approval of certain promising investigational drugs known as Fast Track and Priority Review.

Some have stated the accelerated approvals may be working for certain conditions but it had limited success in developing medicines to treat other rare diseases. As such, we will examine different proposals today that would clarify and improve some of FDA's authorities. While I am open to such proposals, it is important to note that any changes we make must not lower the safety of effectiveness standards by which FDA approves new medicines.

Today we will also discuss the regulation of medical gases. Medical gases are among some of the most widely prescribed drugs and have been in use since before the enactment of the Federal Food, Drug and Cosmetic Act in 1938. Many of these, for example, oxygen, are often used with other medical products such as a device. As I understand it, most of these core gases have been marketed for many years without an approved New Drug Application. According to the industry, medical gases are different than other traditional drugs and should be treated as such. Therefore, they have proposed a new regulatory system for dealing with medical gases that would cover things like good manufacturing practices, labeling, distribution, registration, listing and product tracking requirements. I believe there is a great value to this conversation so that members can understand the issues involved. However, I wonder whether an entirely new regulatory system is the answer.

Development of antibiotic drugs is a critical public health issue. As chairman of this subcommittee last Congress, we held a hearing on the increasing of antibiotic resistance and its threat to public

health. Unfortunately, the Nation's ability to counter this threat could be limited because of the lack of antibiotics being developed. Antibiotics were among the most impactful medical innovations of the 20th century. A routine treatment to combat bacterial infections, they are one of the main contributors in the decline of infectious diseases. But bacteria are living organisms, and as such, as they can and will mutate with time to be able to resist the drugs that have been developed to combat them. We now find ourselves in a situation where our triumph over infectious disease is in jeopardy. More and more bacteria are proving to be resistant to the antibiotics currently on the market.

I am eager to hear from FDA and witnesses today about the proposed legislation that would create financial incentives for companies to develop more antibiotics drugs and spur advancement of these products, particularly whether that approach will help solve the issues our system faces but also what would be the shortfalls of that approach. For example, how do we limit the uses of these new antibiotics so that we don't see the same type of resistance we are seeing now with old medicines?

And one of the more complicated but critical issues is the downstream safety of the U.S. drug supply chain. In order to ensure that we do not have counterfeit stolen drugs entering the supply chain and harming patients, this committee has heard for a long time about the call for greater oversight of the drug supply chain. The need to set up a system that would track and trace the movement of drugs once they enter the marketplace has been the common theme. Just last month, we saw a counterfeit version of the cancer drug Avastin found in the United States. The counterfeit did not contain the medicine's active ingredient, proving to be ineffective, and this is dangerous and in some cases life threatening.

I think we can all agree that Congress needs to get serious about securing the supply chain and that a national system is necessary to prevent these drugs from reaching patients. Some States are beginning to pass their own laws. California, for example, has a law that will go into effect in 2015.

I am interested to hear about the different approaches being proposed, specifically, the positives, negatives and feasibility of each. However, as we contemplate moving forward, we must not rush to legislation. These are really complicated and dense processes, and if we are looking at setting a national standard, it is critical that it be a strong, robust standard that is most beneficial to the consumer.

So just let me close, Mr. Chairman, by thanking everyone. I look forward to our panels today. Your testimony and insight will remain useful in the months ahead. Thank you.

Mr. PITTS. The Chair thanks the gentleman and yields 5 minutes to Dr. Gingrey from Georgia.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, thank you for yielding to me. I am going to confine my remarks to the shortages of antibiotics, and of course, that is the bill that the chairman referred to.

Mr. Chairman, again, I appreciate you holding this hearing and the three panels of witnesses. The need for new antibiotics is well established and beyond question. Antibiotic resistance is a threat to global public health as well as United States national security. Drug-resistant bacteria like those featured in the movie Contagion threaten American patients and troops in much the same way. Whether transmitted from person to person or contracted from biological weapons, the overall threat is the same. As a physician, I understand how important it is that medical providers use antibiotics judiciously, but no matter how judiciously we use the current supply of drugs we have or will have in the coming years, we need more. To quote the testimony of Dr. Janet Woodcock of the FDA, the United States is, and I quote her, "at a critical juncture with regards to drug development. We are in urgent need of new therapeutic options to treat the resistant bacteria that we currently face and we will need new therapeutic options in the future." This critical juncture requires immediate action if we are to prevent a public health disaster from hitting our shores in the next decade.

I want to thank Dr. Woodcock for being here today, and I personally thank Dr. Margaret Hamburg for her leadership on this important issue as the Director of the FDA.

To Dr. Woodcock's testimony, antibiotic resistance cannot be solely solved by the development of new drugs but it also be solved without them. In fact, we can answer every other problem with regard to antibiotic resistance, but if we fail to address the lack of incentives for drug companies and research and development experts and new antibiotic drug development, let me say this emphatically, we will lose this fight.

As a group of bipartisan Members of Congress, my coauthors and I have forwarded H.R. 2182, the Generating Antibiotic Incentives Now, or GAIN Act, to encourage new drug development. The legislation is product of years of thoughtful consideration, and it strikes a balance between the need for drug companies' incentives and the needs and requirements of good public health policy. That balance is attested to in the nearly 50 organizations that currently support our effort. Their testimonials, which I will be entering into the record shortly, underscore the potential that the GAIN Act holds to ensure patients will continue to have the lifesaving medications that they need. Among those we count public health leaders like the Pew Charitable Trust, patient organizations including Kids v. Cancer, medical providers like St. Jude's Children's Hospital in Tennessee, and organizations representing 2.5 million veterans and wounded warriors, among others.

The legislation as drafted focuses incentives on a list of unmet needs and life-threatening pathogens from which infections arise. These pathogens were identified by the Infectious Disease Society of America as looming threats to public health because little or no treatment currently exists to combat the infections that they cause. The legislation also includes, and this is most important, Mr. Chairman. The legislation also includes the ability for the FDA to update this list to meet new and emerging threats so that we continue to encourage the therapeutic options that FDA will testify are needed.

To be clear, drug researchers and manufacturers in early development focus their efforts on identifying products that work against as an identified pathogen as an example including their ability to kill a specific or variety of deadly bacteria. Only after a compound is identified as working against a specific pathogen do the societies then focus on infection sites in the body in order to measure the efficacy of that potential drug.

Some have questioned the need to be so specific with regards to the types of killer bacteria that we are focusing on in the GAIN Act. To that issue, let me read to you a sentence from one of the many support letters we have received. "The GAIN Act definition ensures that unmet medical needs get the attention they deserve in an industry where other therapeutic areas often hold greater commercial promise." However, the incentives for development decrease dramatically if we are unable to know with a high degree of certainty that a product would qualify for the incentives in the GAIN Act in early phase development. In short, our ability to demonstrate to companies the incentives in the GAIN Act as early in the drug development process as possible is the foundation upon which our efforts rest.

Mr. Chairman, I have gone over time. I will go ahead and submit the rest of my comments for the record, and I look forward to the testimony of the three panels of witnesses.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentlelady from Illinois, Ms. Schakowsky, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. JANICE D. SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. I really have just about a minute to say this, but I wanted to put it on the record.

I wanted to say that I strongly support the development of drugs to enhance therapeutic options for patients with rare diseases. There is no question that both patients and their families must cope with unusual and unique issues when they have a rare disease. I can appreciate the desire on the part of patient groups and their families as well as industry to create an accelerated approval for drugs to treat rare diseases. I both understand and support that goal, but I also want to ensure that in seeking to accelerate drug approval that we do not expose patients to unnecessary and unacceptable risks. While I am committed to efforts to accelerate the development of rare-disease drugs, I want to make sure we maximize drug safety efforts and that we do not encourage expedited FDA approval if doing so would jeopardize that goal.

So I am looking forward to hearing you, Dr. Woodcock, on how best to address this issue, and I will yield back my time.

Mr. WAXMAN. Will the gentlelady yield to me?

Ms. SCHAKOWSKY. Of course.

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

Mr. WAXMAN. Thank you very much for yielding to me. We have all the subcommittees scheduled at the same time, and I was trying to get up here as quickly as possible. I am pleased to have this opportunity to make an opening statement because we are going to be looking at some important proposals today. We haven't yet seen the legislative text, but the proposed list of user fee add-ons is long, and as each day passes I am increasingly concerned about whether we will have time to get to a bipartisan agreement on such an ambitious package of bills.

The policies we will be discussing today involve complex public health issues. For us to do a responsible job on these proposals, we need time and we need bipartisan agreement. We should not rush this work. We should prioritize getting it right, not just getting it done, and if we are able to come to a bipartisan agreement in the time available, it makes sense to move them along with the other bills. Otherwise, I hope we can all agree it will be better to wait so that we do not jeopardize the passage of the underlying user fee bills.

Let me turn to some specific proposals. We have learned in a series of hearings this subcommittee held in 2010 that the problem of antibiotic resistance is a dire public health threat and our arsenal of effective antibiotics is running dangerously low. So clearly we need to look at ways to incentivize the development of new antibiotics. The GAIN Act is a good first step at achieving this goal. However, we should ensure that the bill is narrowly tailored to drugs that treat dangerous infections for which we don't have adequate treatments. Otherwise, we risk worsening the problem of resistance. We also need to ensure that the bill mandates that FDA and other agencies involved take steps to ensure that the efficacy of these newly developed antibiotics is preserved once they are on the market.

We will also hear today about FDA's Accelerated Approval system. We can all agree that we want the most effective, innovative medicines to be available at the earliest possible time. So if there are improvements that could be made in the way FDA reviews these medicines, we should consider them. But I am concerned that some of these proposals are driven by unsubstantiated claims that FDA has become too demanding of drug companies, requiring too much data, and thereby allegedly keeping drugs from patients and driving innovation and jobs abroad.

As we have heard at previous hearings, there is apparently no reliable data to back up these claims. To the contrary, as the testimony of Friends of Cancer Research and FDA has shown, FDA actually approves novel drugs faster than its counterparts in Europe or anywhere else in the world. In the past, the National Organization for Rare Disorders has also testified about its study showing that FDA is quite flexible in its requirements for approving orphan drugs.

We want drugs approved as quickly as possible but we want the FDA to do its job, and it is a difficult one. We want to give you

the tools and we want you to have the flexibility to do that job as quickly as possible while meeting the requirements of the law.

I am open to considering whether legislation can help FDA work with companies to get more breakthrough medicines to patients more quickly. However, we need to ensure that any adjustments don't alter FDA's approval standards.

Today's hearing will also examine efforts to improve the integrity of our drug supply chain. This is an important issue. There is a regulatory void at the Federal level because the United States does not currently have laws requiring the tracking and tracing of pharmaceuticals. Consequently, some States have stepped in and enacted their own laws, and we are going to hear today about California, which currently has a law that would mandate one of the most robust pedigree systems in the country. Many have suggested that there is a need for a single Federal system that would preempt these State laws. I believe having a system at the Federal level could make sense if done correctly but I would have grave concerns about preempting a strong State law, especially in California.

Thank you, Mr. Chairman.

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

Our first panel will have just one witness, Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA. We are happy to have you with us today, Dr. Woodcock. You are recognized for 5 minutes for your opening statement.

STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Ms. WOODCOCK. Thank you, Mr. Chairman, and good morning.

Mr. Chairman and members of the subcommittee, I am Janet Woodcock. I am Director of the Center for Drug Evaluation and Research at the FDA, and I really appreciate the opportunity to testify on these important issues that are before the panel.

The mission of the drug program at FDA is to make sure that medicines are of high quality, safe, effective and available. The quality of the United States drug supply has long been taken for granted by, I think, the health care community but the drug supply can be threatened by poor manufacturing practices, by economically motivated substitute, as we saw in the heparin problem, and by counterfeit drugs, all problems that we have observed in the last several years and that are increasingly. The FDA must continue to be vigilant to maintain the quality of drugs in this country, and we must have the property tools to maintain a high-quality medicine supply.

At the same time, health professionals and patients continue to rely on FDA standards for safety and efficacy so that the benefits and risks of medicines are studied and that they are described in the drug label at the time of approval and that we remain vigilant for unexpected side effects once the drugs are marketed. In considering new steps to enhance FDA regulations, we should not diminish the historic protective standards for safety and efficacy that have served our patients so well.

And finally, drugs should be available. The current drug shortage crisis has highlighted how important a reliable drug supply really is. The drug user fee proposals FDA has delivered to Congress are targeted to strengthen the availability of drugs for Americans.

The prescription drug user fee program that Congress has authorized four times already has really assured that the United States is the leader in developing and introducing new important drugs to the public so that Americans have access to that cutting-edge science and to drugs that will treat life-threatening conditions.

The new generic drug user fee proposal is intended to strengthen our generic drug review program that provides access to affordable, high-quality drugs and also addresses FDA oversight of drug quality around the world. And FDA's biosimilars program is intended to provide access to more affordable biologic drugs.

While these FDA programs are strong and successful, it is clear there are continuing challenges in drug regulation, many of which will be discussed at this hearing. I look forward to working with you to find solutions that will benefit our public that we serve mutually. Thank you.

[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

"FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development, and Downstream Pharmaceutical Supply Chain"

March 8, 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 a number of important issues facing FDA, including expediting access to new therapies, efforts to facilitate the development of antibacterial drug products, securing the supply chain for prescription drug products, and the regulation of medical gases.

The Availability of New Therapies

FDA considers the timely review of the safety and effectiveness of New Drug Applications (NDA) and Biologics License Applications (BLA) to be central to the Agency's mission to protect and promote the public health. In the past 20 years, American patients have been provided access to over 1,500 new drugs and biologics, including treatments for cancer, infectious diseases, neurological and psychiatric disorders, and cardiovascular diseases. In FY 2011, FDA approved 35 new, groundbreaking medicines, including two treatments for hepatitis C, a drug for late-stage prostate cancer, the first drug for Hodgkin's lymphoma in 30 years, and the first drug for lupus in 50 years. This was the second highest number of annual approvals in the past 10 years, surpassed only by 2009. Of the 35

innovative drugs approved in FY 2011, 34 met the target dates for review as agreed to in the Prescription Drug User Fee Act (PDUFA).[1]

According to researchers at the Tufts Center for the Study of Drug Development, the time required for the FDA approval phase of new drug development (i.e., time from submission until approval) has been cut since the enactment of PDUFA in 1992, from an average of 2.0 years for the approval phase at the start of PDUFA to an average of 1.1 years more recently.[2]

FDA has steadily increased the speed of Americans' access to important new drugs compared to the European Union (EU) and the world as a whole. Of the 35 innovative drugs approved in FY 2011, 24 (almost 70 percent) were approved by FDA before any other regulatory agency in the world, including the European Medicines Agency. Of 57 novel drugs approved by both FDA and the EU between 2006 and 2010, 43 (75 percent) were approved first in the United States.

A recent article in the journal *Health Affairs* also compared cancer drugs approved in the United States and the EU from 2003 through 2010. Thirty-five cancer drugs were approved by the United States or the EU from October 2003 through December 2010. Of those, FDA approved 32—in an average time of 8.6 months (261 days). The EU approved

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[1] PDUFA was enacted in 1992 and authorizes FDA to collect fees from companies that produce certain human drug and biological products. 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. The current legislative authority for PDUFA expires on September 30, 2012. On January 13, 2012, HHS Secretary Kathleen Sebelius transmitted recommendations to Congress for the next reauthorization of PDUFA (known as PDUFA V).

[2] Milne, Christopher-Paul (2010). *PDUFA and the Mission to Both Protect and Promote Public Health* [PowerPoint slides]. Presentation at the FDA PDUFA Public Meeting, Rockville, MD.

only 26 of these products, and its average time was 12.2 months (373 days). All 23 cancer drugs approved by both agencies during this period were approved first in the United States.[3]

Speeding Access to New Therapies

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.

The most important of these programs are Accelerated Approval, Fast Track, and Priority Review. 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.

[3] "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.

Over 80 new products have been approved under Accelerated Approval since the program was established, including 29 drugs to treat cancer, 32 to treat HIV, and 20 to treat other conditions such as pulmonary arterial hypertension, Fabry disease, and transfusion-dependent anemia. Three of the 30 new molecular entities (NMEs) approved in 2011 were approved under Accelerated Approval. For example, FDA approved Corifact, the first treatment approved for a rare blood-clotting disorder, under Accelerated Approval on February 17, 2011.

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. The purpose is to get important new drugs to the patient earlier. Once a drug receives Fast-Track designation, early and frequent communication between FDA and a drug company are encouraged throughout the entire drug development and review process. The frequency of communication 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.

In 1992, under PDUFA, FDA agreed to specific goals for improving drug review times and created a two-tiered system of review times—Priority Review and Standard

Review. FDA aims to review priority drugs more quickly, in six months, versus 10 months for standard drugs. Priority review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists, while Standard Review is applied to drugs that offer at most only minor improvement over existing marketed therapies. FDA reviewers give Priority Review drugs priority attention throughout development, working with sponsors to determine the most efficient way to collect the data needed to provide evidence of safety and effectiveness. For example, on January 31, 2012, FDA approved Kalydeco (ivacaftor) to treat patients age 6 or older with Cystic Fibrosis (CF) and who have a specific genetic defect (G551D mutation) after a Priority Review. CF occurs in approximately 30,000 children and adults in the United States. The G551D mutation occurs in approximately 4 percent of patients with CF, totaling approximately 1,200 patients in the United States. CF is a serious inherited disease that affects the lungs and other organs in the body, leading to breathing and digestive problems, trouble gaining weight, and other problems. There is no cure for CF, and despite progress in the treatment of the disease, most patients with CF have shortened life spans and do not live beyond their mid-30's. After the results of studies showed a significant benefit to patients with CF with the G551D mutation, ivacaftor was reviewed and approved by FDA in approximately three months, half of the Priority Review period. Ivacaftor will be the first medicine that targets the underlying cause of CF; currently, therapy is aimed at treating symptoms or complications of the disease.

FDA also recognizes circumstances in which there is public health value in making products available prior to marketing approval. A promising but not yet fully evaluated treatment may sometimes represent the best choice for individuals with serious or life-threatening diseases who lack a satisfactory therapy.

FDA allows for access to investigational products through multiple mechanisms. Clinical trials are the best mechanism for a patient to receive an investigational drug, because they provide a range of patient protections and benefits and they maximize the gathering of useful information about the product, which benefits the entire patient population. However, there are times when an individual cannot enroll in a clinical trial. In some cases, the patient may gain access to an investigational therapy through one of the alternative mechanisms, and FDA's Office of Special Health Issues assists patients and their doctors in this endeavor.

We are committed to using these programs to speed therapies to patients while upholding our high standards of safety and efficacy. 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. We are eager to work with Congress in this area, and we note that several of the enhancements proposed for PDUFA V are aimed at expediting the availability of new therapies and providing FDA the scientific understanding necessary to modernize and streamline our regulatory process.

Therapies for Rare Diseases

Speeding the development and approval of safe and effective drugs for Americans with rare diseases is particularly important. Therapies for rare diseases—those affecting fewer than 200,000 people in the United States—represent the most rapidly expanding area of drug development. Although each disease affects a relatively small population, collectively, rare diseases affect about 25 million Americans. Approximately one-third of the NMEs and new biological products approved in the last five years have been drugs for rare diseases. Because of the small numbers of patients who suffer from each disease, FDA often allows

non-traditional approaches to establishing safety and effectiveness. For example, FDA approved Voraxaze (glucarpidase) in January 2012 to treat patients with toxic methotrexate levels in their blood due to kidney failure, which affects a small population of patients each year. Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. Patients receiving high doses of methotrexate may develop kidney failure. Voraxaze was approved based on data in 22 patients from a single clinical trial, which showed decreased levels of methotrexate in the blood. Prior to the approval of Voraxaze, there were no effective therapies for the treatment of toxic methotrexate levels in patients with renal failure.

We look forward to working with Congress on this issue and note that another PDUFA V enhancement includes FDA facilitation of rare disease drug development by issuing relevant guidance, increasing the Agency's outreach efforts to the rare disease patient community, and providing specialized training in rare disease drug development for sponsors and FDA staff.

Facilitating the Development of New Antibacterial Products

Antimicrobial agents have been used in human and veterinary medicine for more than 70 years, with tremendous benefits to both human and animal health. However, because bacteria are so adept at becoming resistant to antibacterial drugs, it is essential that such drugs be used judiciously to delay the development of resistance. Preserving the effectiveness of current antimicrobials and encouraging the continued development of new ones is vital to protecting human and animal health against infectious microbes.

The field of antibacterial drug development is currently facing challenges because of the complexities in designing informative, ethical, scientifically sound, and feasible, clinical trials for studying antibacterial drugs. In addition, there are challenges because of the lack of standardized data on the effect of treatment with antibacterial drugs in certain infections.

FDA cannot overcome these scientific challenges alone, so we have been working to address these issues through guidance development, public workshops, and Advisory Committee meetings. We are working to provide scientifically sound guidance to industry on demonstrating the safety and effectiveness of new antibacterial drugs, particularly on indication-specific trial designs used to study a new drug.

Although the development of new antibacterial drugs is not the entire solution to the important public health problem of antimicrobial resistance, it is a very important part. We are at a critical juncture in this field. We are in urgent need of new therapeutic options to treat the resistant bacteria that we currently face, and we will need new therapeutic options in the future. FDA will continue to work with patients, health care providers, academia, industry, and others within the federal government to modernize the paradigm of antibacterial drug development through guidance and clinical trial designs, and to seek additional solutions to the challenging scientific issues facing the field of antibacterial drug development.

Securing the Supply Chain for Prescription Drugs

As FDA has previously testified before this Committee, the increasingly complex drug supply chain, from raw source materials to finished products for consumers, presents multiple opportunities for the product to be contaminated, diverted, counterfeited, or otherwise

adulterated. Our efforts to secure the supply chain both in the United States and abroad include minimizing risks that arise anywhere along the supply chain continuum, from sourcing a product's ingredients through the product's manufacture, storage, transit, sale, and distribution. A breach at any point in this continuum could lead to dangerous and even deadly outcomes for consumers. Supply chain safety threats also affect manufacturers' bottom lines due to costs associated with both recalls and decreased public confidence.

Counterfeit drugs also raise significant public health concerns, because their safety and effectiveness is unknown. A counterfeit drug could be made up of a substance that is toxic to patients. But even a non-toxic counterfeit drug with a substitute or no active ingredient could prove harmful to patients who take it, thinking that they are taking a lifesaving or life-sustaining medication. In 2003, over $20 million in illegally imported and counterfeit Lipitor (atorvastatin calcium), a popular cholesterol-lowering drug, was distributed throughout the United States. The source and manufacturing methods of the product were unknown and had the potential to endanger patients. Just last month, FDA alerted 19 medical practices in three states that they had purchased unapproved drugs, which may have included a counterfeit version of a widely used cancer drug, from a foreign supplier and distributed through a wholesaler in the United States. While labeled as Avastin (bevacizumab), the imported injectable vials contained none of the medicine's active ingredient. This fake product presents a major public health issue, because some patients may not have received needed therapy.

Implementation of a system to fully track and trace prescription drugs throughout the supply chain would help in combating incidents like the counterfeit Avastin example. Currently there is no complete record of all parties who have been involved with the

distribution of a product after it leaves the manufacturer until it reaches the hands of the patient. This leaves multiple opportunities for counterfeit, adulterated, stolen, or otherwise violative products to be introduced into the supply chain.

While the Food and Drug Administration Amendments Act of 2007 (FDAAA) gives FDA authority to set standards for identification, validation, authentication, and tracking and tracing of prescription drugs, explicit authority to require and enforce the implementation of a national track-and- trace system throughout the supply chain is lacking. In March 2010, FDA issued a final guidance for industry, which describes the Agency's current thinking for standardized numerical identification (also known as serialization) for prescription drug packages. This guidance was the first of several steps that FDA intends to take to implement these provisions of FDAAA. FDA continues to work on developing these standards and held a Track and Trace Public Workshop in February 2011 to obtain public input on the necessary elements to achieve effective authentication and the desirable attributes of a track-and-trace system. Providing the Agency authority to require a cost-effective track-and-trace system for all drug products throughout the supply chain would improve the security and integrity of the drug supply and ensure transparency and accountability of product manufacturing and distribution, whether the product is manufactured domestically or internationally.

FDA Regulation of Medical Gases

Medical gases are among the most widely prescribed drugs in the United States, and some have been in use since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. Medical gases are typically used to treat vulnerable patient populations, including the elderly and the seriously ill, in a range of health-care settings such as emergency

rooms, intensive care units, neonatal care units, ambulance transport, and home/ambulatory use. They are often used in combination with other medical products, such as medical devices.

Medical gases, including those that have been in widespread use for decades, may under some circumstances pose safety and efficacy concerns similar to other new drugs. These gases have been associated with adverse events, and in some cases have been implicated in mislabeling and contamination incidents that have resulted in deaths or serious injuries. Accordingly, as with other drugs, it is critical that the benefit associated with any given medical gas outweighs its risks when used in a particular patient population for a specific purpose, dose, and duration.

CONCLUSION

Thank you for your interest in the important work we do at FDA. We look forward to working with you to continuously improve our processes to enable new products to reach patients faster while maintaining the safety of our drug supply. I am happy to answer questions you may have.

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

Dr. Woodcock, what can we do to expand Accelerated Approval to further help patients including those with rare diseases?

Ms. WOODCOCK. First, let me say that the Accelerated Approval program has been very successful and has brought access, early access to lifesaving drugs to patients with HIV, patients with cancer, and to many patients with orphan and rare diseases. However, we believe more could be done as far as clarity of use of this proposal. We have found that both in the industry, in the academic community and even sometimes within the FDA itself there is confusion about the use of Accelerated Approval. So we believe that additional clarity in the use of this would be very beneficial. We also plan to issue guidance that will also clarify the use of Accelerated Approval and will explain our evidence standards more clear.

Mr. PITTS. Thank you. Despite the success of Accelerated Approval for cancer drugs, I have talked with patients and innovators and investors, and they indicate that some in FDA intend to limit the use of the Accelerated Approval pathway for cancer drugs. This is very concerning to me. As you know, if FDA goes down this path, patient access to important new cancer drugs will be decreased. Investment in new cancer therapies will continue to drop. That would be unacceptable. Rather than limiting the use of Accelerated Approval in cancer, shouldn't we be looking for ways to expand it? Would you please comment on this?

Ms. WOODCOCK. Certainly, and I believe we are looking for ways to expand the use of Accelerated Approval in cancer. For example, we will soon issue a draft guidance on the use of a new surrogate called pathologic complete response, which would be used in high-risk breast cancer as a mechanism to do Accelerated Approval. So I believe that we have been successful in cancer, and in fact, over the last year we have approved cancer drugs using Accelerated Approval, sometimes using what are called historical controls, which means that the drug is treated in patients and their response is compared to what would have happened if they had had standard therapy.

So we are not really backing away from that. However, we have had discussions about the magnitude of the response. What does that mean? That means that if you see in a historically controlled trial, maybe you see a 5 percent response rate or a 10 percent response rate, you really don't know the amount of benefit to the patients, and so that is the level of disagreement that is going on. It is very technical and it is within the oncology community. But please be assured, we are not backing off with Accelerated Approval for cancer. In fact, we would like to find more endpoints we could use for Accelerated Approval.

Mr. PITTS. OK. Thank you. We all agree that it is important to prevent counterfeit drugs from reaching our Nation's patients. What steps is the agency taking to prevent this?

Ms. WOODCOCK. We have for a long time had extensive effort on counterfeits. We are working with our foreign counterparts around the globe to try and identify gaps in the supply chain and inspection coverage and so forth, have early notification between all regulatory authorities when counterfeits are discovered. Our Office of

Criminal Investigations also handles a lot of investigations into counterfeit drugs. However, we do believe that additional authorities are necessary for us to be able to stem this tide.

Mr. PITTS. All right. Now, you mention in your testimony that a system to track and trace prescription drugs through the supply chain would help ensure the integrity of our drug supply. Do you believe the most effective track-and-trace system would involve a uniform standard throughout the country, and what are the elements of a cost-effective system?

Ms. WOODCOCK. Because drugs are shipped all around the country and across State lines, we believe uniform standards are important and we are developing elements of standards that we would publish suggested standards that could be used. The most important features of track and trace are the following. Number one, that you can identify the product as it moves through the supply chain and particularly in real time so that patients aren't being exposed to counterfeits before you discover that they have entered the system, so that is one point. Another point is that modern drug manufacturing makes lots of drugs, in other words, batches, but it isn't like you might think of, you know, what you might compound or whatever. A batch may be a million pills or tablets or more. And so instead of a batch moving through the supply chain on a pallet, OK, a batch would be a lot, would be broken up and go all over the country in different—so a lot—tracking to the lot level is not that helpful, would not be that helpful if we wanted real-time detection, say, drugs that have been stolen from that lot and then diverted and reentering the supply chain or a copy had made of that lot number and then put back into the supply chain at some point. We would not be able to detect that unless we are tracking that lot as it goes along by unit, not by whole lot.

So we recognize that there are tradeoffs between cost of these systems and the benefits that they would provide, but if we want out patients not to get counterfeit drugs, which has happened even recently—they have been administered to cancer patients—we are going to need a system that tracks to the unit level and identifies the movement of the drugs in real time.

Mr. PITTS. The Chair thanks the gentlelady.

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

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Woodcock, I wanted to ask you a question about the GAIN Act and then a couple of questions about medical gases. I think we can all agree that we need to find ways to encourage and facilitate development and approval of important new antibiotics. The GAIN Act is one attempt to achieve that goal. However, I know FDA and others have had concerns about the current definition of which drugs would be eligible for the incentive. I believe that IDSA and others have suggested that GAIN should be limited to new antibiotic for treating serious infections for which there is an unmet medical need. I think the focus on treating serious infections has not been controversial but I wanted to know your views on the other two components, that the antibiotics should be a new chemical or molecular entity and that it should meet an unmet medical

need, if you could just tell me your views on that, and then I am going to get to the medical gases. Go ahead.

Ms. WOODCOCK. A new chemical entity is simply an attempt to make sure that this incentive applies to new drugs that are being developed and not to re-studying older drugs. So I think that particular provision is really up to Congress as far as how that—but what we really need is new molecular entities or new chemical entities that have new mechanisms of action that will be put against these threats.

Now, the second question?

Mr. PALLONE. The other one is that it should meet an unmet medical need.

Ms. WOODCOCK. By definition, we would want it to meet an unmet medical need. People who are facing infections where there is no current satisfactory treatment would meet the definition of an unmet medical need.

Mr. PALLONE. OK. Let me get to the gases, and that is the H.R. 2227. From what I understand, medical gases are regulated by the FDA as drugs. However, because they differ in some ways from most other drugs, FDA has tried to adjust its requirements to fit them and has taken a risk-based approach to enforcement. However, the Compressed Gas Association believes that medical gases are different enough from other drugs that they warrant a new set of regulations. So my questions relate to that. Can you explain how FDA regulates gases now, in particular, the commonalities and differences between your regulation of gases and your regulation of other drugs and the safety profile of gases? And then, you know, as I said, this bill provides for a streamlined process that would deem certain gases approved if the applicant submits a certification that the gas is among certain designated gases that are considered to be well understood and safe. So what is your view on that? And then last, what do you think about establishing a separate regulatory system for gases that covers things like good manufacturing practices, labeling, distribution? Do you think we should have a separate system? I am throwing these all in because we only have 2 minutes, so try to cover it if you can.

Ms. WOODCOCK. Number one, for designation, certain uses of medical gases have been used so long in medicine that they actually didn't fall under the FDA review process that was instituted when the Food, Drug and Cosmetic Act was passed and so technically those uses are unapproved because no applications have been submitted, and so we feel for those traditional medical gases for traditional uses that a designation process would be useful.

As far as a whole new regulatory regime for medical gases on manufacturing, we believe that might not be necessary. We believe we could work with the manufacturers and actually I would commit to working with the manufacturers to develop an appropriate and flexible interpretation of our regulations and their application to medical gases for traditional uses that I think would be mutually satisfactory.

Mr. PALLONE. Obviously, one of the things that they have said to me is if there was some way that you could meet with the Compressed Gas Association to see if there is some way to accommodate

their needs and eliminate the need for legislative action. You seem to be suggesting that. Is that fine?

Ms. WOODCOCK. I would be happy to meet with them personally.

Mr. PALLONE. All right. Let me just ask one thing. Did you respond to the question about the streamlined approval process?

Ms. WOODCOCK. What I said was that some designation process would probably be most satisfactory. These oxygen——

Mr. PALLONE. These are streamlined for the ones that have been around for a while?

Ms. WOODCOCK. Exactly. For all medical gases, we could conceive of high-tech new uses that actually should be studied, but traditionally, giving someone oxygen because they have low blood oxygen, it is really not that controversial.

Mr. PALLONE. So the streamlined would be for the one that have been around?

Ms. WOODCOCK. Yes.

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

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman from Texas, vice chairman of the subcommittee, Dr. Burgess, for 5 minutes for questions.

Mr. BURGESS. I thank the chairman for the recognition.

Dr. Woodcock, always good to see you. The last time we were together, we talked a little bit about drug shortages, and in fact, in October, the President put out an executive order, and you were kind enough to receive myself and my staff out at the FDA about a week or so later. We talked about this. This was early November. Then you came to the committee a few weeks ago and we talked extensively about a particular shortage called Doxil, or doxorubicin. I think sterile methotrexate came up in the discussions as well, and of course, I was very glad to see then shortly thereafter we found a way to circumvent some of the problems with Doxil. There was difficulty in establishing bioequivalency because in order to do the studies to establish bioequivalency meant that the drug had to be taken away from patients who were dependent upon it for therapy, those patients suffering from ovarian cancer who really couldn't afford a lapse in therapy and the FDA didn't really provide a way out of that. So now you have, and I am grateful for that, and that involved actually I guess the use of some of the same compound or similar compound that was available overseas. I am not quite sure how the methotrexate got resolved but I am glad to see that it did.

But you provided us with a really extensive list of drugs that were in shortage, and of course, some of them were sterile injectables, the cancer drugs which are clearly pretty important stuff. So I guess my question to you is—and you have also testified, if I remember correctly, that this is a complex problem. It is not the same thing causing the shortages across the board. So we look at it and say we are going to draft legislation, we are going to fix this problem, we are going to stop it, but it is difficult to do because the problems are so complex and yet your agency had the ability to reach out somewhere and solve these two very serious problems for patients across the country. So I guess my question to you is, what can you do as a regulatory agency to go down that list? Do

you have a task force that is trying to identify the most critical needs, the most critical shortages, get those things, whatever we need to do to get them through the regulatory hoops in a safe and efficient manner and get them delivered to patients of this country?

Ms. WOODCOCK. Yes. We certainly have a shortage team who is really working overtime, and we have augmented that team with additional people. We have looked at every one of the drugs on the shortage list, and if we have had a generic applicant that is pending, we jump the queue. We expedite the review of that application and try to get that approved as soon as possible so that additional sources could be on the market.

In addition, even when a shortage is impending, we think there is an impending shortage, we will start looking at alternative supply? Can other manufacturers in the United States ramp us their production? We contact them, we talk to them. Are there X U.S. manufacturers with acceptable facilities and product that could increase their production and thus cover the U.S. drug supply as well? So we do all this. Despite this, we are still experiencing shortages, primarily because a lot of facilities in the United States making sterile injectables have been experiencing manufacturing problems.

Mr. BURGESS. Yes, let me ask you about that because some of the manufacturing problems actually relate to the company's ability to get a return on investment or even break even in the process, and they say look, it is not worth it to us to revamp our manufacturing line for this product. Is there anything you can do at the FDA as far as providing the incentives so that company will stay in the business because then they don't have to go through the whole reapplication and all of the approval process again?

Ms. WOODCOCK. We have very little to do with the economic side of drug production and reimbursement. We focus on making sure that the facilities and processes are in place to make a reliable drug product. I don't think that cutting corners in manufacturing sterile drug products is the answer because the problems that these facilities have experienced are significant. They include endotoxin contamination, bacterial contamination and particulates in injectables, and these types of problems do not result in useable sterile injectables.

Mr. BURGESS. I need to interrupt you because time is running short. I have some things I am going to submit in writing about conflicts of interest, stuff we have covered before to some degree and I have got some new questions. But can you update us on—the New England Journal of Medicine had an article probably back in 2010 or maybe 2009 on the curious case of colchicine, and colchicine is a drug that has been around for 3,000 years to treat gout and familial Mediterranean fever, as I recall, and because of some things that happened at the FDA, suddenly this drug spiked in price and was becoming more difficult for patients to receive.

Ms. WOODCOCK. That situation still continues. The FDA has something called an Unapproved Drugs Initiative, and we are trying to get drugs that are not approved by—there is no approved version by the FDA into the fold of proper drugs in the United States, and sometimes these efforts do have unintended consequences and I certainly I have heard—I am a rheumatologist. I

certainly have had from a large amount of the community and patients about this particular issue of affordability of this medicine. We are trying to make the balance between availability and affordability and the ability to assure a reliable supply of a drug. When drugs are not FDA approved and they are simply on the market, there are many opportunities for problems. So we try to walk this path, but believe me, we are very aware of the problems that have been created for patients.

Mr. BURGESS. Thanks, Mr. Chairman. I will yield back.

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

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

Dr. Woodcock, I want to ask you about Accelerated Approval. There is a bill by Mr. Towns and Mr. Stearns, and Dr. Maraganore will discuss this on our second panel. The act would clarify and improve FDA's ability to use surrogate and clinical markers for the Accelerated Approval pathway. Dr. Allen, also on our second panel, describes in his testimony another approach for breakthrough products. This approach would ensure that the FDA works closely with companies in helping them develop clinical trial designs that would expedite approval of important drugs showing promise in early trials. And then we also have the Infectious Disease Society of America, and they submitted testimony for the record that discusses yet another approach, and this one is focused on facilitating approval of drugs that would treat serious diseases in limited populations.

My biggest concern in looking at these proposals is whether they do or have the potential to change the approval standard, which is something I hope we can all agree we don't want to do. Can you briefly, because I have another set of questions, describe for us what you see as any benefits of these proposals as well as any concerns you have with any of them?

Ms. WOODCOCK. On Accelerated Approval, as I said earlier, I think the main point is a clarity of our ability to approve drugs on an early clinical endpoint or a surrogate endpoint that is reasonably likely to predict clinical benefit. But I do not believe that changing the standards for safety and effectiveness would be a benefit to patients. So it is more about clarifying what approval mechanism we can use but not changing the evidentiary standard.

As far as breakthrough therapies, I have had several people who are involved in the AIDS epidemic and the development of drugs to address that epidemic say to me if we had treated that as business as usual, we would never have solved this epidemic, we would have never gotten effective drugs available. And HIV is not the only terrible, life-threatening problem that people face. So breakthrough therapy is not about the approval standard. It is about getting all hands on deck when we find—when early in development a product is found to potentially have a tremendous benefit, a life-changing benefit in a serious disease. And we all should get together at that point—this is my professional opinion—and figure out the most effective and efficient way to evaluate that therapy to see if it really has the promise that it appears to have, so if it does, patients will not have to wait years to have that therapy.

Mr. WAXMAN. Do we need legislation to do that?

Ms. WOODCOCK. No. However, I believe that designating that as a very important process that the agency would have would provide benefit.

Mr. WAXMAN. I want to ask you about the integrity of our drug supply chain and preventing safety crises. You have already indicated you think that we ought to require drugs to be tracked all the way down to the unit level, not only require that supply chain entities track a lot number of the product. I want to ask you about the question of the pharmacies because in the coalition bill, the pharmacies are essentially excluded from that proposal, and I am concerned about preempting State laws as strong as California's. So I would like to know FDA's views of the importance of the differences between the two models. You have already talked about the supply chain. You might just repeat it again, but what do you think about excluding the pharmacies? And if we have a single Federal system, how important do you think it is that pharmacies be included and that drugs are traced to the unit level instead of the lot level?

Ms. WOODCOCK. If our goal is to prevent our patients from receiving counterfeit drugs before they receive them rather than going back and trying to reconstruct what happens after they have received counterfeit drugs and we have detected them, then we are going to have to have a system that is a real-time system that tracks the drugs through the system down to the pharmacy level. Why? Because diversion and insertion of counterfeits can occur at any point during the drug distribution chain and you leave a big gap there for the criminals, and we know there are a lot of criminals out there outside of our country who want to make profit by putting counterfeit drugs into our distribution chain or by stealing drugs, perhaps adulterating them and then reinserting them back.

Mr. WAXMAN. You would include pharmacists and pharmacies?

Ms. WOODCOCK. We have had some cases like that.

Mr. WAXMAN. This is going to be expensive, and I suppose that the technology advances quickly and gets cheaper over time, so we need to work as robust a system as possible but realize that we have to phase it in, I suppose.

Ms. WOODCOCK. Right. I think that there are costs, significant costs, associated with it. You have to balance the costs against the potential benefits, and I think we have to ask ourselves, are we going to wait until we have a mass sort of poisoning from insertion of counterfeit drugs or when we assume those costs, is the benefit worth the costs. There is no doubt that there will be costs to all members in the supply chain to do this.

Mr. WAXMAN. Thank you, Mr. Chairman.

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

Mr. SHIMKUS. Thank you, Mr. Chairman. Welcome, Dr. Woodcock.

My first question is kind of really a response to an answer you gave to Congressman Pallone on the discussion on the GAIN Act. I am an original sponsor on Dr. Gingrey's bill along with Dianna DeGette, Anna Eshoo, Gene Green and other members, and we have been working a long time. The intent is to list the biggest

unmet needs, the pathogens, and then allow you all to add new pathogens.

Ms. WOODCOCK. Yes.

Mr. SHIMKUS. I think in the question-and-answer period, the concern was removal and flooding of the market with ones that aren't needed. We have concerns about that, and let me address the concerns. The intent is not obviously to try to remove folks. First of all, there is really not a market unless there is something that really happens bad. So our concern is someone developing an antibiotic to meet a specific pathogen that is on the list and then all of a sudden they get pulled off the list. Now, what incentive would that be for anyone, really, anyone, to go in and try to take advantage of this process?

Ms. WOODCOCK. Well, I would say that the FDA has various processes such as orphan drug designation and other designation processes now that we operate, and generally the simpler the rules, the easier these are to operate administratively. We also have a process that was established under the user fee——

Mr. SHIMKUS. Yes, and I was real involved with the orphan drug provisions, but really, the question still is, there will be a debate, it sounds like, on both sides on the ability to remove. I think our basic analysis is, one, there is no need to remove; two, it is really a disincentive. And I would ask you to look at that provision from the folks who want to innovate, those who may have already spent a lot of money and then all of a sudden it is off the list.

Let me go to my other questions. As Dr. Frieden of the CDC testified in 2010, antibiotic resistance is a public health problem of increasing magnitude and finding effective solutions to address this problem is a critical focus of the CDC activities. Is it safe to say that you feel similarly that finding solutions to addressing this problem is a critical focus of your activities?

Ms. WOODCOCK. Yes.

Mr. SHIMKUS. And how important is new drug development in the fight against this public health threat?

Ms. WOODCOCK. It is crucial.

Mr. SHIMKUS. Thank you. It kind into this whole obviously the GAIN Act in which we are focused on today, part of it we are focused on today.

One of the issues is on the ventilator-assisted pneumonia example where our rules are that it can't be tested if the population has already received antibiotics so a lot of this testing occurs overseas, and then as I have stated numerous times, there is a concern with that because you are there, you are testing, you are spending money. You may segue into the E.U. system and then we may lose that population. How do we get around, or is that exclusion of testing a population that has never received antibiotics, is that really a hurdle that we can't overcome in our testing aspects here in the United States?

Ms. WOODCOCK. We are currently in discussions both with the industry and the Infectious Disease Society of America and other interested parties about what the drug development paradigm should be for multi-drug-resistant organisms, and we actually feel that a much abbreviated development program, a very small development program which would be an incentive for developing these

types of antibiotics would be highly feasible if in fact it were linked to the concept of good antibiotic stewardship post market.

Mr. SHIMKUS. So there is hope?

Ms. WOODCOCK. Absolutely, but I think that is something that we need to discuss more as far as the good antibiotic stewardship aspect of this.

Mr. SHIMKUS. Great. Thank you, Mr. Chairman. I yield back my time.

Mr. PITTS. The Chair thanks the gentleman and recognizes the Ranking Member Emeritus, Mr. Dingell, for 5 minutes for questions.

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

Dr. Woodcock, welcome.

Ms. WOODCOCK. Thank you.

Mr. DINGELL. One way to address the threats in a supply chain is to know who is responsible for the pharmaceutical product at each point in the supply chain. I am sure you agree with that. Yes or no?

Ms. WOODCOCK. Yes.

Mr. DINGELL. As you know, the PDSA proposal would provide for lot-level traceability. Would lot-level traceability be helpful in identifying where in the supply chain a violation occurred?

Ms. WOODCOCK. It might be difficult due to the size of lots.

Mr. DINGELL. But you would be better off than you are now?

Ms. WOODCOCK. I think the benefits of doing that would have to be balanced against the costs of even enacting such a system.

Mr. DINGELL. Now, some have advocated for unit-level traceability over lot level so that you could track individual products and identify threats before incidents occur. Would unit-level traceability be helpful in the instance of contamination or entry of a counterfeit product? Yes or no.

Ms. WOODCOCK. Yes.

Mr. DINGELL. Now, one concern I continue to have is contamination or diversion of prescription drugs by persons outside the supply chain. Would lot-level traceability help the FDA to identify the path of a contaminated product as it traveled through domestic distribution?

Ms. WOODCOCK. Only partially, and would have to be reconstructed I think after the fact.

Mr. DINGELL. What would be the obstacles or the difficulties there?

Ms. WOODCOCK. Because large numbers of any given lot are manufactured, then determining if some counterfeits of that lot were added at some point would be difficult unless you had real-time tracking and you kept account of the volume.

Mr. DINGELL. Now, in the instance of contamination or diversion, would lot numbers be helpful if a particular lot of drugs traveled through multiple distributors and reached multiple pharmacies?

Ms. WOODCOCK. It would be helpful in retrospectively determining perhaps the point of entry of the contaminated version but it would not be helpful, I don't think, in real time.

Mr. DINGELL. Thank you. Now, I happen to believe that manufacturers, distributors and dispensers should keep accurate and

thorough records detailing who is buying and selling a drug throughout the distribution chain. I am sure you agree with that.

Ms. WOODCOCK. I agree.

Mr. DINGELL. Would it be helpful to FDA to have each entity in the supply chain—manufacturers, wholesale distributors, dispensers—accountable for the authenticity of their product here?

Ms. WOODCOCK. Yes.

Mr. DINGELL. Now, again, I want to commend the industry for their work on the Rx proposal. Traceability is a vitally important tool in securing our drug supply and one I believe would complement the drug safety proposal that I have been pushing. I look forward to working with industries and my friends on the committee to ensure that traceability proposals move through this committee in a way that will best achieve the mutual goal of preventing counterfeit and contaminated products from entering our drug supply.

Doctor, thank you for your presence.

Ms. WOODCOCK. Thank you.

Mr. PITTS. The Chair thanks the gentleman and yields to Dr. Gingrey from Georgia for 5 minutes for questioning.

Mr. GINGREY. Mr. Chairman, thank you.

Dr. Woodcock, thank you. The GAIN Act is squarely focused on serious bacterial pathogens with equally serious unmet medical need including Gram-negative bacteria, a specific one that was dubbed Iraqibacter due to the propensity of infections among our wounded soldiers in Iraq. It is an increasing cause of hospital-acquired infections in intensive care units leading to tens of billions of dollars in expenses and it is increasingly resistant to numerous drugs, leading to a high number of fatalities. It can show up as pneumonias, complicated skin infections, tissue infections, and indeed even septicemia, which is better known in common parlance as bloodstream infections. Most worrisome, Doctor, the pipeline for novel therapies against something like Iraqibacter is slim to virtually nonexistence. Now, Dr. Fauci, the Director of the CDC, testified before this committee in April of 2010 that our focus should be on infections derived from problematic pathogens like this Gram-negative bacteria Iraqibacter. Dr. Woodcock, do you agree with Dr. Fauci that encouraging drug development to combat infections that arise from Gram-negative pathogens like Iraqibacter is an appropriate role for Congress and the FDA?

Ms. WOODCOCK. Absolutely.

Mr. GINGREY. According to the Web site of the FDA, you have launched several initiatives to combat antibiotic resistance including encouragement of the development of new drugs, vaccines and improved tests for infectious diseases. Yet many public health organizations, patient groups and drug companies have stated that greater incentives are needed if we hope to increase new antibiotic drug development. Do you believe that current FDA actions are enough to encourage the numbers of new antibiotics we need to meet the growing public health threat that antibiotic resistance poses?

Ms. WOODCOCK. No, clearly it is not enough.

Mr. GINGREY. So the provisions in the GAIN Act, very specifically, Dr. Woodcock, like increasing the time of exclusivity from 10

to 15 years and to be very specific in regard to the pharmaceutical community that are developing these new drugs and biologics, do you agree that they need to know ahead of time that all of this cost and expense and innovation and research and development that literally the rug is not going to be pulled out from under them by some indiscriminate decision after the fact that the FDA might make in regard to a list of pathogens that we already know are causing serious medical illnesses no matter where they might strike, whether it is in the bloodstream or in the lungs causing pneumonia or in the skin causing things like necrotizing disease, which indeed can be deadly. So my question in regard to all of this is, don't you agree, or do you disagree that being very specific about the pathogens and things like MRSA, methicillin-resistant staph aureus, and a lot of these Gram-negative bacteria, enterococcus and things like that, these need to be designated on the front end, and of course, the Director of the FDA has the opportunity or the Secretary of HHS, you know, to add additional things to the list. So comment on that for us.

Ms. WOODCOCK. Certainly. It is obvious, and we know from experience that industry needs, because of the cost and the risk, a very clear pathway to market, and that is a big incentive if that is very clear and laid out, so that is extremely important. I agree with that.

As far as how to do this in this specific instance I think we are more administratively looking at how administratively you would set such an incentive up, and because antibiotic resistance evolves rapidly and this is a dynamic field and actually many organisms are implicated in this, it would seem that in general for Congress to set up some more general criteria and then have FDA designate that way. We then could make agreements with companies about the designation at the time they come and talk to us about their development program and what the pathway would be. So it just seems that stipulating in the statute certain things rather than what the criteria might be, maybe setting the criteria would be a better way to go.

Mr. GINGREY. Mr. Chairman, I realize I am over time, but let me just conclude here.

Dr. Woodcock, I think you answered my question or my premise in the affirmative, and this is sort of what I think Mr. Shimkus was getting at in regard to the ability to add to, and you have that in the GAIN Act. You have that ability as things develop to be able to add to the list but I think the list at the outset in the law should be very specific.

So with that, Mr. Chairman, I yield back, and thank you for your patience.

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

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

As I said in my opening statement, I am interested in the balance between hurrying the drugs that we need to market and making sure that we protect safety. It seems to me that most of the claims about FDA's poor performance have in fact been disproved, and you described quite powerfully how effective FDA has been at

using its current Accelerated Approval authorities. So it is surprising to me that we are still talking about the need for yet another accelerated approval pathway, and I hope we can all agree that we have to be somewhat cautious in this area. At the very least, we need to ensure that we don't force FDA into a position where its approval standards are lowered and the agency ends up force to approve ineffective or unsafe drugs, which is in no one's interest.

So let me just ask you this. Does the FDA have concerns about H.R. 4132, the FAST Act, for example, having the potential to lower the approval standards?

Ms. WOODCOCK. Well, we would look forward to working with Congress and the committee on any given language and providing technical assistance. I think it is important to not lower the standards for safety and efficacy and to be clear in the language while we do support the idea of clarifying what can be used as the basis for Accelerated Approval.

Ms. SCHAKOWSKY. And do you take into account the fact that people who are gravely ill are in fact willing to take more risks, and what is the mechanism for doing that, for separating out those individuals who in fact willing to take some more risks?

Ms. WOODCOCK. Well, we always balance benefit and risk. Obviously, cancer drugs aren't as safe as headache drugs, and so we are taking that into account. The user fee program, the prescription drug user fee program that is before Congress now, will have as part of it a formal mechanism where we go out and solicit patient input into these tradeoffs, especially for diseases that aren't well understood and so that we can understand how much risk people are willing to take for a certain amount of benefit. And then after marketing, typically there is patient information and we are moving toward getting uniform patient information in the United States so that when people get a prescription drug, they understand the benefits and the risks and they can make that tradeoff for themselves because individual values differ.

Ms. SCHAKOWSKY. And do we distinguish between people who are pretty desperate to try things as opposed to sort of for the general population? I mean, is there any flexibility in that way?

Ms. WOODCOCK. Well, what we typically do is have—the drug is studied and so understand the magnitude of the benefit and then all the risks are described, and then it is determined between the patient and the physician when that treatment decision is being considered that they would discuss both the upsides and downsides of the therapy so the patient can make an informed choice.

Ms. SCHAKOWSKY. So the obligation then of the FDA is to just make sure that there is complete disclosure of the—let me ask you this. Do you need more authorities to speed new therapies to market?

Ms. WOODCOCK. No, we don't think that new authorities are needed. Perhaps some clarification might be useful but, no, we feel that we can get safe and effective drugs, that more risk is tolerated for cancer, for life-threatening diseases and so forth. We can get these therapies to the patients with an appropriate balance of benefit and risk.

Ms. SCHAKOWSKY. Thank you. Unless someone wants my time, I yield back.

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

Mr. MURPHY. Thank you for being here, Dr. Woodcock. I always appreciate your testimony and find you to be a very trustworthy source, and thank you for your leadership.

I want to ask you about drug shortages in particular. From what I understand, many of these are cancer drugs. Can you explain why we are facing shortages in cancer drugs?

Ms. WOODCOCK. I think the HHS Assistant Secretary for Planning and Evaluation report has the best explanation of what happened. Most of these cancer drugs are off-patent sterile injectable drugs and they were very few manufacturers in the United States making them, sometimes only one manufacturer. They were making a large list of sterile injectables also. And they developed some manufacturing problems. Multiple manufacturers developed problems making the drugs and had to shut down their lines or interrupt production, and this, as I said last time, is a perfect storm where this all sort of came together. Multiple manufacturers of the few that existed in the United States for sterile injectables all developed problems. As the report shows, many manufacturers had added newer injectable drugs that probably had increased profit margins as they came off patent, added them to their list and so they were producing a very extensive list of products, and when they ceased production or had to restrict their production, then there were other places to turn in the United States.

Mr. MURPHY. Is the FDA taking any steps to change some of these things to address the shortage issue?

Ms. WOODCOCK. Yes. The steps we take, number one, we work with the manufacturers. We do everything we can to keep these particular shortage drugs in production. We have even gone to the lengths of testing the drugs, see if the particles could be filtered out and allowing them to be shipped to the patients, to the doctors if they would filter them at the time of use. OK. That isn't what you would want of a drug supply but it is better than not having those drugs available. We also expedite any applications for making additional sites or additional manufacturers who want to make these drugs, we expect their generic drug applications. If we have to, we work with foreign suppliers who may be making these drugs and see if they can ramp up their production and import temporarily into the United States to cover the shortage situation, and we have some of that happening right now.

Mr. MURPHY. Let me ask about another area. I am a psychologist by training and worked in pediatrics also. I served in the Navy and worked with PTSD and TBI veterans. And one of my concerns is also the abuse of drugs. It is a sad story that we have to address, and of course, the abuse of drugs also is associated with some shortages. Some of the stimulant medications used for attention disorder, for example, have shortages. That hurts those who really need them but there is also people using that shouldn't be having them and other class II and III drugs that are being used too, and I wonder about addressing these as other issues of taking care of

the shortages by doing such things on a Federal level, an issue I am working on legislation much like a couple of States have done, and that is, requiring a photo ID when people pick up some of these drugs. It is not difficult and it is not a secret that someone could take a Medicare patient's prescription, take it to the drugstore, fill it for Vicodin or something else, and next you see Grandpa can't find his prescription, the doctor writes another one, and these things go on. It is similar for abuse of some of the drugs used by children which they may sell or they may redistribute, and I get particularly concerned when we have so many veterans who end up self-medicating themselves out of their pain. So I wondered if this is something that in terms of States, I think Maine and North Carolina have put in some laws in effect requiring a photo ID or a designated person to pick up the drug when that person can't do it. If you know of any research in terms of, is this addressing some of the issues with regard to reduction of abuse or at least helping a situation where drugstores are not put in the middle of basically becoming suppliers to drug abuse networks?

Ms. WOODCOCK. Thank you. We are doing quite a bit in this area. The Administration last year announced an initiative to try to combat the epidemic of prescription drug abuse in the United States, and we have multiple efforts that we are working on. I am not familiar with the results of the research on photo ID and what impact that might have on decreasing diversion to people who are not supposed to get the prescriptions, but it is clear that we need to take additional measures to control this epidemic. It is ravaging some communities.

Mr. MURPHY. I appreciate that. I am aware of one chain, CVS, requires on their own a photo ID, contacting the physician, asking for the diagnosis to verify a number of these steps in that process, and that helps, and I certainly know when I have talked to some pharmacists and they languish with this idea that say someone shows up with a prescription, we are filling it but worried that it is actually being abused, so I would love to be able to with you more in addressing this, and I do appreciate your dedication to this. Thank you so much.

I yield back.

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

Mr. CASSIDY. Hi, Dr. Woodcock. How are you?

Ms. WOODCOCK. I am fine. Thanks.

Mr. CASSIDY. I have concerns about online pharmacies. As I gather, they are unregulated. It is kind of a Wild West out there and lots of issues associated with them. The latest article in the Wall Street Journal of course is on online pharmacies. Now, we have heard testimony recently about abuse potential drugs and the problems of prescription drug abuse. So both adulterated and abuse potential. Can you comment on the role of online pharmacies in these two issues?

Ms. WOODCOCK. It is clear that online pharmacies can be——

Mr. CASSIDY. By the way, just to be clear, there are legitimate and illegitimate pharmacies, so I am sorry, continue.

Ms. WOODCOCK. No, I agree with that. There are obviously sites around the world that can pose as pharmacies and are distributors and may introduce improper drugs or provide drugs without a prescription or sometimes provide drugs that are counterfeit to people. The VIPPS program, which certifies certain Internet pharmacies as appropriate and has criteria, is one guide to consumers. We have educational material that we have tried to put out and tried to educate patients and consumers on what proper procedures might be for ordering drugs over the Internet because unguided they may well run into harm.

Mr. CASSIDY. Now, is it fair to say, though, that—now, first, I am a physician who happens to be a Congressman who is married to a doctor, and I had never heard of the VIPPS program until today, which is not a criticism of FDA. Frankly, it is a criticism of my wife. Just kidding. But that said, is it fair to say that the current mechanism has some inadequacy if even someone who theoretically would be educated such as I does not know?

Ms. WOODCOCK. I think it is a very difficult problem. The whole system was set up for brick-and-mortar pharmacies. Our whole control system was set up that way. Now we have the Internet. As you said, it is the Wild West, and definitely it is putting American patients and consumers in harm's way.

Mr. CASSIDY. I am struck that as we speak about unit-level tracking, really, that doesn't mean anything if I am buying online from something which I think is legitimate but which is illegitimate and I am getting an adulterated drug from another country. Is that a fair statement too?

Ms. WOODCOCK. Absolutely.

Mr. CASSIDY. So until we can actually do something about the online pharmacies, we are going to continue to have a leaky bucket allowing things to come in which should not?

Ms. WOODCOCK. That is correct.

Mr. CASSIDY. Any sense of how much of the drugs that are abuse potential being used here would come in through online pharmacies? Do we have a sense of the scope of the issue?

Ms. WOODCOCK. We do not.

Mr. CASSIDY. And do we have a sense of how many of the online pharmacies are legitimate versus illegitimate?

Ms. WOODCOCK. Again, the Internet is a very rapidly changing and evolving——

Mr. CASSIDY. Fair answer. Now, let me ask you again, I am aware of the issue of valid prescriptions versus invalid and would just like your comments upon that.

Ms. WOODCOCK. Well, I think the definition of a valid prescription is an important keystone of any efforts and we have to do that in light of, you know, now the electronic prescribing and phone prescribing and so forth, but I think that is a very important component.

Mr. CASSIDY. So the valid prescription, just for those who may not be familiar with it, currently pertains to a controlled substance but not to an uncontrolled substance. So I can get an antihypertensive, which doesn't require a valid prescription, but the Vicodin, I would, but the absence of the requirement of a valid

prescription for the antihypertensive may mean I get an adulterated drug. Fair statement?

Ms. WOODCOCK. Yes, if you happen to order from an inappropriate pharmacy on the Internet.

Mr. CASSIDY. So ideally, we would come up with—we apply the definition of valid prescription—I am just saying this to see if you would agree—the definition of a valid prescription which would apply both to controlled and non-controlled substances?

Ms. WOODCOCK. Yes.

Mr. CASSIDY. I know we are about to vote and so I yield back to other members. Thank you.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman from New Jersey, Mr. Lance, for 5 minutes for questions.

Mr. LANCE. Thank you very much, Mr. Chairman, and I respectfully request my opening statement be placed into the record.

Mr. PITTS. Without objection, so ordered.

[The prepared statement of Mr. Lance follows:]

The Honorable Leonard Lance
Opening Statement
Subcommittee on Health
March 8, 2012
FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain

Thank you Mr. Chairman.

Today the subcommittee will consider several issues related to the reauthorization of the Prescription Drug User Fee Act or PDUFA. One issue that I believe deserves attention under PDUFA is the regulation of medical gases.

For more than a century doctors, nurses, dentists and home health care providers have used medical gases to treat their patients. In fact medical gases are prescribed to more than a million patients every day.

Medical gases make up a unique class of drug products that are different from traditional pharmaceuticals in many ways.

For example, the six medical gases that make up 99 percent of the prescriptions in the U.S. – oxygen, nitrogen, nitrous oxide, carbon dioxide, helium and medical air – are mostly derived from the air we breathe every day.

Yet despite these differences the Food and Drug Administration (FDA) consider medical gases under the same regulatory system as pharmaceutical drugs.

And while the FDA has a long history of using its enforcement discretion and exempted medical gases from its new drug application process recent changes to federal policy has left both manufacturers and patients uncertain of the future of FDA-approved medical gases.

I have introduced the Medical Gas Safety Act with my colleague Congressman Chris Murphy to address this regulatory uncertainty. Our bipartisan legislation will provide the FDA with the tools it needs to develop a regulatory system that takes into consideration the unique nature of medical gases.

The bill will provide the necessary regulatory clarity that will ensure access of these life-saving products for patients while protecting jobs.

I look forward to working with the FDA and the medical gas industry to bring more certainty in this area.

Mr. LANCE. Thank you, Mr. Chairman.

I want to follow up on questioning from Congressman Pallone regarding medical gases, and I know that you are working on this issue. As I understand it, the six medical gases that make up 99 percent of the prescriptions in the United States—oxygen, nitrogen, nitrous oxide, carbon dioxide, helium and medical air—are mostly derived from the air that we breathe. The FDA has a long history of using its enforcement discretion in exempting medical gases from its New Drug Application process but recent changes to Federal policy, I believe, have left both manufacturers and patients uncertain of the future of FDA-approved medical gases.

The legislation that Congressman Pallone referenced, legislation I have introduced, the Medical Gas Safety Act, which is bipartisan in nature—I have introduced it with my colleague, Congressman Murphy, Chris Murphy—tries to address this situation in a bipartisan capacity. I want to work with you in this regard. Can you comment on where you might be going regarding this issue?

Ms. WOODCOCK. Certainly. We feel also that there are long-recognized and medically acceptable uses of these traditional medical gases and that some designation would be very useful rather than having an application process, approve something we already know, all right?

Mr. LANCE. Yes.

Ms. WOODCOCK. But as far as some of the other issues relating to the manufacturing process and so forth, we believe that our regulations are sufficiently flexible that we can work out an approach without additional legislation that would be mutually satisfactory to the industry and to the FDA.

Mr. LANCE. Thank you, Doctor. I know that your staff has some reservations about developing separate, current good manufacturing practice regulations for the medical gases. Codifying current regulatory experience with medical gases is, in my judgment, the best way to resolve some of the confusion, and the Compressed Gas Association, which is the safety-standard-setting organization for the industry, has offered its full resources to assist in the rulemaking process. I want to thank you for your willingness to meet and work with the association, with the staff here on this committee, with my staff on this issue.

I do not necessarily think that guidance can remove the requirements from existing regulations, so I do think that some changes in the regulations are necessary, and I respectfully request that we continue to work together on this issue as PDUFA is reauthorized.

Ms. WOODCOCK. We will be happy to work with you.

Mr. LANCE. Thank you very much, Mr. Chairman, and I yield back the balance of my time.

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

Mr. LATTA. Well, thank you, Mr. Chairman, and Dr. Woodcock, thanks for being with us today. If I could just kind of go back to a question that was asked by Dr. Burgess and one also that was asked by Dr. Murphy. One of the questions that Dr. Burgess asked, and I want to make sure that I wrote it down correctly when you said that, that he asked what can the FDA do to help incentivize businesses to stay in business in the manufacturing process, and

your answer was at the time that, you know, your focus is really on that reliability. And Dr. Murphy then had asked a question in the same vein because there is a lot of questions about there on the drug shortages, that the question as to manufacturing problems and that you had stated that in trying to address that problem you would work with the manufacturer. Is there a difference between trying to keep people in business and those companies out there that are manufacturing right now?

Ms. WOODCOCK. Can you rephrase the question?

Mr. LATTA. Well, the first part of the question is that you had said that as Dr. Burgess had asked the question, he asked what can the FDA do to help incentivize businesses sustain manufacturing processes of producing the product, and you had said in response to his question that your only focus is really on the reliability end and not on trying to keep them in business. So that would be a company out there that, you know, might be trying to incentivize somebody to stay in that type of a process in manufacturing but Dr. Murphy had asked the question as to if there are manufacturing problems and keeping pills out there or other drugs in the manufacturing stream to get to the patients and that you would say that you would work with those manufacturers. I am just trying to figure out what the difference between the two is on the reliability and working with them.

Ms. WOODCOCK. My understanding of Dr. Burgess's question was, did we help with the economic incentives, and we don't have really any role in the economic aspects of drug production and marketing and so forth. We do work with manufacturers to try to keep them manufacturing shortage drugs or any other drugs and we try to work with manufacturers to keep them manufacturing a reliable supply of the medicines that they produce. I do believe that the generic drug proposal that is before Congress right now will help with this because it will help us clear out our backlog of generic drug applications that have decreased the predictability of a generic drug review process and hopefully we may encourage more entrants into that process. So we do work with them but we are not involved in the marketing and reimbursement or any of those aspects.

Mr. LATTA. And also in answer to some of Dr. Murphy's questions, could you define when you say you would help filter?

Ms. WOODCOCK. Yes. Manufacturers of sterile products—that would be that go into your vein—we are finding they had particles in their products. That is bad. That is very bad but they can go into your lungs and get stuck and so forth, so it is not acceptable. So when those were in shortage, rather than say you can't send them out, we tested to make sure that a filter would take out the particles and not take out the drug, and then we let the drugs be shipped with a filter so that at the point of delivery, they could be filtered and get the particles out and the patient would still get that drug rather than have it be in shortage. So I think that is an illustration that we try to work with the manufacturers to keep these drugs out there.

Mr. LATTA. And also, other countries that are out there that have experienced drug shortages, how have they met the shortages like say in Europe?

Ms. WOODCOCK. They work much the same way that we do, and we work with the European regulatory authorities to try to make sure the international drug supply remains robust. So they take the same sorts of actions we do.

Mr. LATTA. Again, just one last question, if I may. With the 1981 flu pandemic that might have killed between 25 to 75 million individuals, it is being pretty much attributed now not to the flu but to tuberculosis, and in January of this year, a completely 100 percent drug-resistant form of TB was identified in India that would not be treatable with any known antibiotic. What is the FDA doing right now to try to prevent that from getting to these shores?

Ms. WOODCOCK. Yes. Well, we certainly are working with the coalition that is working on developing new drugs for multi-drug-resistant tuberculosis. This is a serious threat. We recognize it and we are doing everything we can. Our combination investigational drug guidance, which is realize is very technical, that we put out that showed how you could develop several investigational drugs together to deal with a threat such as this I think is helpful in this effort. And as I said earlier, we believe that if provisions for good antibiotic stewardship were able to be instituted and we were sure that such a drug would only be used only for drug-resistant tuberculosis, we could have a very small development program that would allow that drug to get on the market. That would provide, I think, a tremendous incentive to manufacturers to get into this space and develop drugs for multi-drug-resistant TB.

Mr. LATTA. Thank you, Dr. Woodcock.

Mr. Chairman, I yield back.

Mr. PITTS. The Chair thanks the gentleman. That concludes the questions. Go ahead, Dr. Cassidy, for one follow-up.

Mr. CASSIDY. Mr. Lance brought up H.R. 2227, medical gas. Just to confirm that this would not apply to already approved substances, correct?

Ms. WOODCOCK. Correct.

Mr. CASSIDY. They would continue to be regulated as they currently are?

Ms. WOODCOCK. That is my understanding.

Mr. CASSIDY. Thank you. I yield back.

Mr. PITTS. Thank you, Dr. Woodcock, for appearing before the subcommittee this morning. We really appreciate your testimony and answering all of our questions. That concludes panel one.

Ms. WOODCOCK. Thank you.

Mr. PITTS. We will now call panel two to the witness table, and I would like to thank all of these witnesses for agreeing to testify before the subcommittee today. I would like to quickly introduce our expert panel. First of all, Dr. John Maraganore is CEO of Alnylam Pharmaceuticals. Dr. Jeff Allen is the Executive Director of Friends of Cancer Research. Dr. Barry Eisenstein is Senior Vice President of Science Affairs at Cubist Pharmaceuticals. Dr. John Powers is the Assistant Clinical Professor of Medicine at George Washington School of Medicine. And Mr. Michael Walsh is the President of LifeGas. Mr. Walsh is appearing on behalf of the Compressed Gas Association.

Again, we thank all of you for coming this morning. We have your prepared statements. Dr. Maraganore, we will begin with you. You are recognized for 5 minutes to summarize your testimony.

STATEMENTS OF JOHN MARAGANORE, CHIEF EXECUTIVE OFFICER, ALNYLAM PHARMACEUTICALS; JEFF ALLEN, EXECUTIVE DIRECTOR, FRIENDS OF CANCER RESEARCH; BARRY I. EISENSTEIN, SENIOR VICE PRESIDENT, SCIENTIFIC AFFAIRS, CUBIST PHARMACEUTICALS; JOHN H. POWERS, ASSOCIATE PROFESSOR OF MEDICINE, GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE; AND MICHAEL WALSH, PRESIDENT, LIFEGAS, ON BEHALF OF COMPRESSED GAS ASSOCIATION

STATEMENT OF JOHN MARAGANORE

Mr. MARAGANORE. Thank you, Chairmen Upton and Pitts and Ranking Members Waxman and Pallone. It is my privilege to provide testimony before the subcommittee today. My name is John Maraganore and I am the Chief Executive Officer of Alnylam Pharmaceuticals.

As a scientist and a businessman, I have over 25 years of experience in biopharmaceutical research and development. I serve on the board of several biotechnology companies and I am also an advisor to Third Rock Ventures and a member of the Biotech Industry Organization Governing Board.

Founded in 2002, Alnylam is a small, nonprofitable biotechnology company located in Cambridge, Massachusetts. We are developing new medicines based on the science of RNA interference, or RNAi, which is a major breakthrough in biology that was recognized by the award of the 2006 Nobel Prize for Medicine or Physiology.

Today our company has 120 employees who are working on a pipeline of innovative medicines that could truly be transformative in the lives of patients afflicted with a number of genetic diseases including diseases such as systemic amyloidosis, hemophilia, sickle cell anemia, severe hypercholesterolemia, Huntingdon's disease, liver cancer and also respiratory syncytial virus. If we are successful in our efforts, we can create a whole new class of medicines and treat disease in a fundamentally different way.

I am here today to discuss the importance and the benefits of Congressman Stearns' and Towns' Faster Access to Specialized Therapies, or the FAST bill, which would modernize the Accelerated Approval pathway at the Food and Drug Administration. The Accelerated Approval pathway, implemented in 1992 by the FDA and codified by the Congress in 1997, has indeed been a great success story but only in part. While its applicability has been largely limited to certain disease areas, mainly cancer and HIV/AIDS and certain situations, the pathway has stimulated an explosion of investment and innovation in those diseases and has brought immense benefit to patients suffering from those diseases. There are several reasons why the Accelerated Approval pathway should be expanded and in fact modernized.

First, as I just mentioned, the Accelerated Approval pathway has worked but only in part. That is, it has been largely limited in practice to drugs that treat cancer and HIV/AIDS along with a

handful of other situations. While this is great news for patients afflicted with cancer and HIV/AIDS, it is not good news for patients suffering from other serious and life-threatening diseases. Nothing in the words of the current statute limits the Accelerated Approval pathway to just oncology and HIV/AIDS. In fact, the statute is worded broadly but the current FDA practice leaves many other treatments for rare and serious conditions effectively excluded from the pathway. We need certainty about how the FDA can apply Accelerated Approval in the future by ensuring that the pathway is available for all therapies which treat serious or life-threatening conditions by enacting the FAST Act.

Second, it is important that the ability to utilize the Accelerated Approval pathway is both better understood by sponsors and more consistently applied by the FDA. This is especially true when it comes to FDA-accepted clinical endpoints including those that could be measured earlier than irreversible morbidity or mortality to demonstrate a reasonable likelihood of overall clinical benefit. While the pathway allows for approval based upon effects on clinical endpoints that are reasonably likely to predict clinical benefit, in practice, the lack of clarity surrounding such approval options has led to a very limited use of Accelerated Approval by sponsors and the FDA.

Third, it is time to have an expanded and modernized Accelerated Approval pathway that incorporates the remarkable advances in the life sciences that have and will provide an unprecedented understanding of the underlying biological mechanisms and disease pathogenesis. These advances can enable novel drug development strategies that employ leading-edge methodologies and tools such as biomarkers and novel clinical trial designs that can overall improve how we implement Accelerated Approval. The FAST bill would achieve all of these objectives described above by expressing the sense of Congress that the FDA should utilize the Accelerated Approval pathway as fully and as frequently as possible while maintaining, very importantly, FDA's safety and effectiveness standards and by codifying, modernizing and expanding FDA's Accelerated Approval pathway with four targeted revisions.

I thank you very much for your time and attention and I urge Congress to consider the FAST Act.

[The prepared statement of Mr. Maraganore follows:]

TESTIMONY OF JOHN MARAGANORE, PH.D.

CHIEF EXECUTIVE OFFICER, ALNYLAM PHARMACEUTICALS

HOUSE COMMITTEE ON ENERGY & COMMERCE, SUBCOMMITTEE ON HEALTH HEARING ON:

"FDA USER FEES 2012: HEARING ON ISSUES RELATED TO ACCELERATED APPROVAL, MEDICAL GAS, ANTIBIOTIC DEVELOPMENT AND DOWNSTREAM PHARMACEUTICAL SUPPLY CHAIN"

March 8, 2012

Chairmen Upton and Pitts, and Ranking Members Waxman and Pallone, it is my privilege to provide testimony before this Subcommittee today. My name is John Maraganore and I am the Chief Executive Officer of Alnylam Pharmaceuticals. As a scientist and businessman, I have over 25 years of experience in biopharmaceutical research and development. Prior to Alnylam, I served as Vice President of Strategic Product Development for Millennium Pharmaceuticals where I worked on products to treat cancer and cardiovascular, autoimmune, and metabolic diseases. Prior to Millennium, at Biogen (now Biogen Idec, Inc.) I invented and led the discovery and development of Angiomax™, a direct thrombin inhibitor that is used as an anticoagulant in over 750,000 patients every year. Currently, I serve on the Immunology Advisory Council of the Harvard Medical School and am a member of the Biotechnology Industry Organization Governing Board. I also serve as a board member of several innovative biotechnology companies that are focused on finding new medicines for cancer, autoimmune disease, and rare genetic diseases, and I am also an advisor to Third Rock Ventures.

Alnylam is a small biotechnology company located in Cambridge, Massachusetts. We are developing new medicines based on the science of RNA Interference, or RNAi, a major breakthrough in biology that was recognized by the award of the 2006 Nobel Prize for Medicine or Physiology to certain academic scientists. We were founded in 2002 and have invested over $500 million to date in our R&D efforts. Today, we have 120 employees who are working on a pipeline of innovative medicines that could be transformative in the lives of patients afflicted with certain genetic diseases like systemic amyloidosis, hemophilia, sickle cell anemia, severe hypercholesterolemia, and Huntington's Disease. We also have therapeutic programs targeting the treatment of liver cancer and a lung infection caused by respiratory syncytial virus, the leading cause of pediatric hospitalization every year. All told, four of our programs are in

clinical testing stages, but RNAi technology affords the potential for an even greater number of programs to be advanced to patients. Indeed, if we're successful in our efforts, we can create a whole novel class of medicines that treat disease in a fundamentally new way.

I am here today to discuss the importance and benefits of Congressmen Stearns' and Towns' *"Faster Access to Specialized Therapies" (FAST)* bill, which would enhance the Accelerated Approval pathway at the Food and Drug Administration (FDA). The impact FDA's approval processes for new drugs and biologics has on innovation in the discovery and development of new treatments for diseases cannot be overstated. There is no question that protecting patients from harm is a critical component of FDA's mission. But so too is establishing regulatory processes that enable the timely development and availability of new safe and effective therapies for patients suffering from serious and life-threatening diseases. In a time when the U.S. medical innovation ecosystem is facing severe strains and increased global competition, it is imperative that FDA's policies and practices find the right balance between these two objectives to ensure we are able to deliver the next generation of breakthrough treatments and therapies.

Importance of Expanding and Modernizing the Accelerated Approval Pathway

The Accelerated Approval pathway was implemented by FDA in 1992 in response to patient groups who, after engaging the public in a dialogue about benefits of new HIV/AIDS treatments, were successful in advocating for earlier access to these life-saving medicines. Accelerated Approval allows for earlier approval of new drugs that provide a benefit for patients with serious and life-threatening diseases based on a new product's effect on surrogate or clinical endpoints that are deemed "reasonably likely to predict clinical benefit."[1] Under Accelerated Approval, FDA can approve the marketing of a drug to seriously ill patients based on earlier evidence of effect with a commitment from the sponsor to conduct further post-market studies to confirm and define the degree of clinical benefits to patients.

The Accelerated Approval pathway has been a great success story, in part. While its applicability has been largely limited to certain disease areas (mainly cancer and HIV/AIDS) and certain situations, the pathway has stimulated an explosion of investment in innovation in those

[1] 21 C.F.R. § 314.500; 21 C.F.R. § 601.40

diseases, and has brought immense benefit to patients suffering from these diseases. In HIV/AIDS, for example, there are now over 20 new medicines on the market. In oncology, FDA has granted Accelerated Approval to 49 new indications for 37 novel oncology drug products since 1995.[2]

However, there are several reasons why the Accelerated Approval pathway should be expanded and modernized. First, it is important that the ability to utilize an accelerated pathway is better understood by sponsors and more consistently applied by FDA. This is especially true when it comes to FDA accepting clinical endpoints, including those that can be measured earlier than irreversible morbidity or mortality, to demonstrate a reasonable likelihood of clinical benefit. While the pathway, which was codified in 1997, allows for approval based upon effects on clinical endpoints that are reasonably likely to predict clinical benefit, in practice the lack of clarity surrounding such approval options has led to very limited use by sponsors and FDA.

Additionally, the Accelerated Approval pathway has been largely limited in practice to drugs that treat cancer and HIV/AIDS, along with a handful of other situations, leaving many other rare and serious conditions effectively excluded from the pathway and creating confusion among sponsors on how to apply the pathway to these indications. While studies such as the National Organization for Rare Diseases (NORD) 2011 report show that FDA applied flexibility and allowed for more limited packages of data for a majority of the approved drugs for non-cancer orphan drugs, it is not always clear to sponsors when or how these approaches will be accepted by FDA.[3] As NORD Chairman Sasinowski has stated, "It would be helpful for such flexibility and importance to be recognized in a formal FDA policy, and for FDA officials to incorporate and recognize that flexibility in a systematic way in their evaluations of each new therapy in development and under FDA review for Americans with any rare disease."[4] It is equally important that flexibility is applied in a systematic way for treatments for products for other serious and life-threatening diseases beyond cancer and HIV/AIDS.

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[2] Dr. Paul Kluetz. ODAC. February 8, 2011, the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC)

[3] Sasinowski, Frank J. "Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs." National Organization for Rare Diseases, October 2011.

[4] "Landmark NORD Study Concludes FDA is Flexible in Reviewing Therapies for Rare Diseases." NORD Press Release, 11 October 2011. http://www.rarediseases.org/news-events/news/fda-flexibility-2011

Second, while I have discussed the importance of expanding disease areas where an Accelerated Pathway could be applied, today there is significant uncertainty over how the FDA intends to apply the Accelerated Approval pathway in the future, and this uncertainty is directly impacting investment in innovative new therapies. In 2011, only 3 of the 35 New Molecular Entities approved by FDA and only 3 of 13 therapies that were granted "Fast-Track" designation utilized the Accelerated Approval pathway.[5] Concerns over utilization of Accelerated Approval have become most acute for those developing cancer drugs. For the past two decades, cancer has attracted more investment capital than any other disease, and potential breakthrough anti-cancer medicines in the pipeline today vastly outnumber those for other therapeutic areas.[6] One of the main reasons for this has been FDA's historical approach of effectively balancing the benefits and risk to approve new cancer treatments. However, since late 2009, there appears to be a fundamental re-evaluation by FDA of the standards for approval of new cancer therapies. The resulting uncertainty is impacting investment in oncology drugs. In fact a 2011 National Venture Capital Association (NVCA)/Medical Innovation and Competitiveness Coalition (MedIC) survey showed that 39% of venture capitalists expect to decrease investments in cancer drugs over the next three years.[7]

Actions and public statements over the past year from FDA's Office of Oncology Drug Products have introduced significant uncertainty over how the FDA intends to apply the Accelerated Approval pathway for cancer drugs. For example, at an Oncology Drugs Advisory Committee (ODAC) meeting in February 2011 and other settings, FDA has raised fundamental questions about the range of situations in which single-arm studies (*i.e.*, studies without a randomized control group, typically using tumor response rate as primary endpoint) and studies using measures of disease progression (such as Progression Free Survival) as primary endpoint should be sufficient to support Accelerated Approval for cancer drugs. Notably, of the 32 novel cancer drugs approved by the FDA from 2003 to 2010, 14 obtained Accelerated Approval, of which 11 were based on single-arm studies without a control group.[8] Additionally, a recent analysis by

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[5] "FY 2011 Innovative Drug Approvals." FDA. November 2011. http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm278358.pdf

[6] Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

[7] NVCA/MedIC Survey. Vital Signs. October 2011.

[8] Johnson, John R., et. al. "Accelerated Approval of Oncology Products: The Food and Drug Administration Experience." JNCI, Vol. 103, Issue 8. 20 April 2011.

BIO and BioMedTracker of cancer clinical trials conducted between 2004 and 2011 showed that more complex randomized, double blind, and multi-arm trials were not statistically more likely to translate into a successful Phase III clinical trial than single-arm open-label trials.[9] Thus while it is appropriate to continually review and debate merits of endpoints and clinical trial designs, it must be recognized that a decision to, for example, narrow the situations where single-arm studies can be used to support Accelerated Approval in oncology would effectively represent a reversal of what has arguably been the most successful policy of the past two decades, in terms of speeding important therapies to patients and encouraging investment in innovative new treatments. In making such a profound change in direction, the FDA must consider the realities of oncology drug development and the needs of patients who have little time to wait for their breakthroughs. We must have policies that focus on how we can more efficiently and effectively deliver potentially life-saving medicines to patients – Accelerated Approval has done this historically and should strive to do so even more in the future. In oncology, the FDA appears right now to be moving in exactly the wrong direction. A critical element of the FAST bill is the clear message that it sends: that the sense of the Congress – reflecting the values of the American people – is that FDA should strive to use the Accelerated Approval pathway more for the benefit of patients, not less.

Third, it is time to have an expanded and modernized Accelerated Approval pathway that incorporates the remarkable advances in life sciences that have been, and will continue to be, made, including genomics, molecular biology, and bioinformatics, which have already provided an unprecedented understanding of the underlying biological mechanisms and pathogenesis of disease. These advances can enable novel drug development strategies that employ leading edge methodologies and tools such as biomarkers, pharmacogenomics, predictive toxicology, clinical trial enrichment techniques, and novel clinical trial designs like adaptive clinical trials. Improving clarity of when and how these tools can be utilized in an Accelerated Approval pathway will not only incentivize drug development for serious and life-threatening diseases but encourage the development and utilization of additional pharmacogenomic tools and methodologies that will create even more efficient, targeted, and personalized drug development strategies.

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[9] "Oncology Clinical Trials – Secrets of Success." BIO and BioMedTracker, 24 February 2012. http://www.biotech-now.org/business-and-investments/2012/02/oncology-clinical-trials-secrets-of-success

FAST Bill Provides Critical Reforms to the Accelerated Approval Pathway

The FAST bill would achieve all of the objectives described above by expressing the Sense of the Congress that FDA should utilize the Accelerated Approval pathway as fully and as frequently as possible while maintaining FDA's safety and effectiveness standards, and by codifying, modernizing and expanding FDA's Accelerated Approval pathway with four targeted revisions. First it would empower FDA to consider a broad range of surrogate and clinical endpoints, including endpoints that can be measured early in the clinical trial process, and endpoints applicable to a wider array of diseases and conditions. Second, it would encourage FDA to consider a wider array of supporting evidence, in addition to clinical trial evidence, to help inform the Agency's assessment of whether there is a reasonable basis to predict clinical benefit. Third, the bill would ensure that FDA takes into consideration the severity or rarity of the condition and the adequacy of any alternative treatments. And lastly, the bill would increase the transparency, predictability, and consistency of the review process by ensuring that FDA develop new guidance and revise existing guidance and regulations to clarify the scope and process for utilizing the expanded Accelerated Approval pathway, including specifically for rare diseases. Nothing in this bill would alter FDA's efficacy or safety standards. These important reforms would create a robust Accelerated Approval pathway that would enable the safe and expeditious development of the next generation of modern medicines to treat particularly dire conditions.

There are many examples where the FAST bill and modernization of Accelerated Approval can have an impact in the development of new medicines. For example, Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disease characterized by severe muscle atrophy and weakness. The disease generally manifests early in life and is the leading genetic cause of death in infants and toddlers. A number of biomarkers exist that allow for assessment of drug activity in SMA patients, but none would currently be considered sufficiently validated today to serve as a surrogate endpoint for Accelerated Approval. However, there are several clinical measures in SMA that can also provide an indication of drug effect in relatively short-term clinical trials. Under an enhanced Accelerated Approval pathway, a demonstration of a favorable effect on one of these so-called "intermediate clinical endpoints" could be judged by FDA to be reasonably likely to predict a clinically meaningful benefit. This would allow for a relatively rapid

Accelerated Approval of SMA therapies, with an obligation by the sponsor to conduct further studies to further confirm the clinical benefit.

Another example is Sickle Cell Anemia, a genetic blood disorder afflicting millions of people around the world with a concentrated U.S. incidence in African-Americans. This disease is caused by mutations in the hemoglobin gene that cause red blood cells to "sickle" and obstruct blood vessels, causing pain and organ damage. New medicines are emerging that are aimed at correcting or altering the hemoglobin gene defects and these could be made available to patients faster if their approval employs the use of biomarkers. Under the FAST bill, FDA will be encouraged to modernize the Accelerated Approval pathway to make full use of such biomarkers and other emerging scientific tools, and to clarify the pathway to Accelerated Approval for novel treatments for diseases like Sickle Cell Anemia.

PDUFA V and Additional Legislative Proposals

As a small biotechnology company CEO, I would like to take a moment to discuss how important timely reauthorization of PDUFA V is to the United States' biotechnology industry. PDUFA V will enhance the drug development and review process through increased transparency and scientific dialogue, advance regulatory science, and strengthen post-market surveillance. The commitment made by FDA in the PDUFA V technical agreement to a philosophy that timely, interactive communication with biotechnology and life science companies during drug development is a core Agency activity will be of great value, especially to small biotechnology companies such as mine. Most importantly, from the standpoint of innovative companies, our hope is that PDUFA V will provide patients and doctors with earlier access to breakthrough therapies.

My testimony today focused on enhancing the Accelerated Approval pathway. There are other proposals being considered by this Committee that I also believe would serve to improve our ability to develop and deliver innovative medicines. FDA's mission statement should be updated to reflect the Agency's critical role in advancing innovation. This would encourage FDA to apply its rigorous standards in the most innovation-friendly manner possible, by striving to reduce the time and cost of drug development wherever possible, and by incorporating modern

scientific advances into review practices to ensure that innovative treatments and therapies are made available to the patients who need them. And lastly, reforming Advisory Committee conflict of interest rules to provide FDA with greater flexibility and discretion to select the most appropriate advisors, consistent with the rules that apply to other federal agencies, would help ensure that FDA decisions are informed by the best available scientific experts and in the best interest of patients.

Fostering Medical Innovation in the United States

It is imperative that we have policies that encourage research and development of the next generation of treatments and cures. Policies being considered by the committee, some of which I have highlighted today, as well as timely passage of the Prescription Drug User Fee agreement, would go long way in fostering medical innovation in the United States. While America has developed more cures and breakthrough medicines than any other country and is home to over 2,500 biotech companies, this is not a position that will be sustained without a concerted policy focus on supporting and incentivizing the next frontier of biomedical discoveries, treatments, and cures. There have recently been a few headlines touting increased investment in the biomedical field. However, these headlines oversimplify the actual state of affairs. The NVCA recently released their fourth quarter 2011 numbers for venture financing in biotechnology in the U.S. While the numbers showed an overall 18% increase in investment from 2010 to 2011, this is not reflective of the situation that most small, innovative biotechnology companies are facing.[10] The 2011 investment in biotechnology is 12% lower than the peak we saw in 2007. Additionally, first round venture deals in 2011 fell below 100 for the third time in a decade and the total number of venture financing deals is down 8% since 2010. Most importantly, especially to small innovative companies, the number of venture-funded early-stage companies fell 19%.[11] The number and quantity of investments moving away from early-stage innovative projects is a very disturbing trend that has been growing over the past few years. In fact the number of first-time financing for life sciences companies is at its lowest level since 1996.[12]

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[10] NVCA/PWC MoneyTree Report: Q4 2011. Data provided by Thomson Reuters.
[11] "Venture Capital increases in 2011, but…" Inside BIO Industry Analysis. 24 January 2012. http://www.biotech-now.org/business-and-investments/inside-bio-ia/2012/01/vc2011
[12] NVCA/PWC MoneyTree Report: Q4 2011. Data provided by Thomson Reuters.

Over the past year we have seen several long-time investment funds announce they will no longer be investing in the medical science sectors. The October 2011 survey conducted by the NVCA and MedIC showed that 40% of venture capitalists expect to decrease investment in biopharma over the next three years, three times as many as the number who expect to increase. This same survey showed that 61% cited regulatory challenges at the FDA as the main reason for reducing investments.[13] This is not entirely surprising given that the time and costs to develop a novel drug have continued to increase over the past decade. In fact, today, it requires an average of 10 to 15 years and $800 million to over $1 billion to develop a new drug, and not only is that cost increasing, it is increasing at an alarming rate.[14][15][16][17] In part this increase in cost can be attributed to the increased complexity of regulatory requirements. For example, between 1999 and 2005 the average length of clinical trials grew by 70%.[18]

In addition to fiscal constraints here in the U.S., we are facing unprecedented competition from around the globe to be the leader in biomedical research. In 2008, China pledged to invest $12 billion in drug development,[19] and in 2011, the Chinese government named biotechnology as one of seven industries that will receive $1.7 trillion in government funding over the next five years.[20] The European Union's Innovative Medicines Initiative is pumping $2.65 billion into Europe's biopharma industry[21] and India's Bioconnect initiative has funded over 200 new biopharma projects.[22]

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[13] NVCA/MedIC Survey. Vital Signs. October 2011.
[14] "Returns to R&D on New Drug Introductions in the 1980s." Journal of Health Economics 13, no. 4 (1994): 383-406
[15] H.G. Grabowski, J. Vernon, and J.A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," Pharmacoeconomics 20, supp. 3 (2002): 11–29
[16] J. Dimasi and H Grabowski J "The Cost of Biopharmaceutical R&D: is Biotech Different?" Managerial and Decision Economics no 28 (2007): 469–79
[17] Munos, Bernard. "Lessons from 60 years of pharmaceutical innovation." *Nature Reviews Drug Discovery* 8, 959-968 (December 2009).
[18] Tufts Center for the Study of Drug Development. 2008. "Growing Protocol Design Complexity Stresses Investigators, Volunteers." Impact Report. 10.1.
[19] Daverman, Richard. "China Launches 'Mega Program' to Fund Drug Development." ChinaBio Today. 9 November 2008. http://www.chinabiotoday.com/articles/20081109
[20] Buckley, Chris. "China to invest US$1.7 trillion over 5 years in 'strategic sectors': US official." The China Post. 23 November 2011. http://www.chinapost.com.tw/business/asia-china/2011/11/23/323724/China-to.htm
[21] Hodgson, John. "€2 billion IMI launched with European pharma." *Nature Biotechnology 26*, 717-718 (2008).
[22] Dandekar, Vikas. "India Draws Lessons From China To Help Foster Biotech Industry." PharmAsia News. 7 February 2012.

This is a time where everyone involved in researching and developing new medicines needs to step up their game. It is industry's responsibility to choose product candidates carefully with a focus on medicines that really matter, and to conduct scientifically valid clinical trials. It is equally important that FDA, as the regulator and ultimate arbiter as to whether promising medicines are made available to patients, has transparent and consistent processes in place that are understood by the patients, medical researchers, industry and its investors. Additionally, it is critical that the FDA engender an environment that is able, in a timely manner, to efficiently and predictably review innovative medicines and allow for the use of modern scientific tools and methodologies that are more efficient and better enable FDA to make determinations of benefit vs. risk. It is also imperative that drugs are reviewed in the context of the patients' needs and disease being treated. And finally, it is essential that FDA take into account the ever-increasing time and cost of drug development, and strive to ensure safety and efficacy in a manner that minimizes that time and cost, thereby speeding important new therapies to patients and encouraging continued investment in innovative treatments for disease.

The U.S. biotechnology industry is poised to be a major driver in an innovation-driven economy and we offer real solutions to our most pressing health care needs: curing disease, reducing costs, increasing quality, and ensuring that people enjoy not only longer lives, but better and more productive lives. Last year we witnessed several promising events: FDA approved 35 novel drugs marking the most approvals in over a decade; and biopharmaceutical companies successfully brought to market remarkable therapies to treat hepatitis C, melanoma, lung cancer, lupus, cystic fibrosis, and a broad range of rare genetic disorders. These advancements in patient care represent the leading edge of the next generation of biotechnology innovations. That said, as I have described, these successes can only continue and increase if we have a policy strategy – an innovation environment – focused on fostering these types of medical breakthroughs. I believe that encouraging scientific dialogue between sponsors working innovative products and the FDA earlier in the drug development process and aggressive strategies by the Agency to encourage the utilization of modern approaches to clinical research and development will serve to not only incentivize innovation but most importantly enable us to deliver game-changing solutions to address our nation's most critical public health needs.

Conclusion

Implementing an enhanced Accelerated Approval pathway, coupled with the new provisions in PDUFA V, will result in dramatic improvements for patients facing life-threatening diseases. These reforms are critical to improving health care in this country. Thank you for the opportunity to share my thoughts with you today.

Mr. PITTS. The Chair thanks the gentleman.

We are presently voting on the floor. We are going to try to get through a couple more of you. Dr. Allen, you are recognized for 5 minutes.

STATEMENT OF JEFF ALLEN

Mr. ALLEN. Thank you. Good morning, Chairman Pitts, Ranking Member Pallone and members of the subcommittee. I am Jeff Allen, Executive Director of Friends of Cancer Research, a think tank and advocacy organization based here in Washington. I would like to thank the staff of the committee who have worked very hard in putting together this important hearing. It is an honor to be here today.

While compelling progress continues to be made within the field of oncology, there is much more to be done. This year, cancer will claim the lives of over 570,000 Americans. This, Mr. Chairman, is roughly equivalent to every citizen in your home county of Lancaster, Pennsylvania.

With such a profound toll, improved ways to combat cancer and other diseases are desperately needed. While there are many factors that make development of new drugs complex, assessments of the process often focus on the FDA. Critics have frequently portrayed the FDA as slow and inefficient compared to other countries. However, our research reveals that FDA is approving anticancer drugs in a more timely fashion than the European counterpart. In fact, since 2003, FDA has approved 42 new cancer medicines versus just 32 by the EMA. Of the 28 common approvals, all were available to U.S. patients first.

A cornerstone of the FDA's standard for approvals was established in 1962 by Congress requiring that all new drugs demonstrate not only their safety but also efficacy. Without this requirement, American patients would have continued to have been given medicines that actually provided no improvement to their health. As this committee seeks to optimize and improve FDA practices and maintain its standing as the global leader, the requirement that new drugs demonstrate both safety and efficacy must be upheld. While the need for new treatments is immense and the challenge is significant, the solution is not to arbitrarily lower this important standard that has been in place for 50 years.

In 1992, as science progressed, and in acknowledgement of an increased public health need, regulations were developed to establish the Accelerated Approval mechanism. This is shown to be an important tool used by the FDA to uphold the rigorous scientific standards while facilitating timely access to lifesaving treatments. For example, in oncology, Accelerated Approval has been used for over a third of new cancer drug approvals since 1999. However, since 2007, the number of oncology drugs approved through this mechanism has decreased.

In order to optimize the use of this tool, Congress should take action to enhance Accelerated Approval to ensure that it is applied consistently, efficiently and effectively. This is not to suggest in any way that the standards of safety of efficacy should be altered but rather to examine additional opportunities in which Accelerated Approval is the optimal approach.

Today, much like at important times throughout recent history, the FDA needs an updated mechanism to respond to the rapid advancement of science. With the expansion of knowledge about the biological basis of complex disease, new targeted therapies are being developed. For these new treatments that show remarkable benefit early in development, the traditional approach may not be appropriate. Currently, there are no clear guidelines to expedite subsequent studies that would generate the needed evidence and minimize the number of patients who would need to be assigned to the current standard of care.

In order to address this, Congress should establish a mechanism that would allow the FDA to designate a new compound that shows substantial clinical activity in early-phase trials as a breakthrough product. Upon designation, the sponsor, working closely with FDA, would develop trial designs to abbreviate or combine traditional phases of development. This would avoid giving larger numbers of patients a potentially harmful or ineffective drug as part of a control arm while maintaining current safety and efficacy standards. This establishment of this new designation would help FDA respond to highly innovative new medicines quickly and consistently across the agency as well as to communicate and encourage drug developers to pursue trial designs that are able to show potential benefit earlier in development.

I conclude my remarks today by reiterating that rigorous FDA standards cannot be compromised. The FDA should be given the ability to respond to cutting-edge science and the most promising therapies through an enhanced Accelerated Approval mechanism and a breakthrough product designation.

I thank you for your time and I am happy to answer any questions you may have.

[The prepared statement of Mr. Allen follows:]

FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain

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

Jeff Allen, Ph.D
Executive Director
Friends of Cancer Research

March 8, 2012

FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain

Testimony of Jeff Allen, PhD, Executive Director, Friends of Cancer Research

Good morning, Chairman Pitts, Ranking Member Pallone, and Members of the sub-committee. I am Dr. Jeff Allen, Executive Director of Friends of Cancer Research, a cancer research think tank and advocacy organization based here in Washington. I would like to thank the staff of this committee who have worked very hard in putting together this important hearing. It is an honor to testify before you today and provide our perspective on several vital mechanisms that the U.S. Food and Drug Administration (FDA) uses to get a new drug or biological products to patients.

While compelling progress has been made within the field of oncology, there is much more to be done to alleviate the current cancer epidemic and profound suffering it causes. It is estimated that, in 2012, over 1.6 million Americans will be diagnosed with some form of cancer. As a result, our healthcare system will be strained an additional $226 billion.[1] Yet tragically, cancer will claim the lives of 571,950 mothers, fathers, grandparents, sisters, brothers, and friends, this year. This, Mr. Chairman, is roughly the equivalent of every citizen in your home county of Lancaster, Pennsylvania.[2]

With such startling statistics and profound toll on human health, improved ways to combat cancer are needed as quickly as possible. Unfortunately, advancements in basic science do not always translate into new treatment as rapidly as many would desire. In fact, recent estimates indicate that it could take upwards of 12 years and over $1 billion to develop a new cancer drug.[3] While there are many factors that make development of new drugs complex and increasingly expensive, assessments of the process often focus on the U.S. Food and Drug Administration (FDA).

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[1] The American Cancer Society: http://www.cancer.org/Cancer/CancerBasics/economic-impact-of-cancer Accessed 3/1/12

[2] http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029819.pdf Accessed 3/1/12

[3] Adams, C. P. and Brantner, V. V. Health Economics, 19 (2010), 130–141. doi: 10.1002/hec.1454

Today, I would like to describe some of the current standards and mechanisms employed by the FDA for new drug review and approval, explore how these tools have been used to date, and propose a new tool to ensure that the most promising new medicines reach the market as quickly and safely as possible.

Standards to Protect and Promote Health

The role of the FDA is to protect and promote the health of the American public by ensuring the safety, effectiveness, and security of medical products, devices, food, and cosmetics.[4] The authority and tools to fulfill this responsibility has evolved over time. For example, in 1962 President Kennedy signed the Kefauver-Harris Amendments into law amending the Federal Food, Drug and Cosmetic Act to require that new drugs demonstrate not only their safety but also efficacy in order to be approved for marketing.[5] Without this requirement, American patients would have continued to have been given medicines that actually provided no improvement to their health and gave them false hope. **As this committee seeks to optimize and improve FDA practices in reviewing new treatments, the requirement to demonstrate both safety and efficacy must be upheld.** While the need for new treatments is immense, and the challenges significant, the solution is not to arbitrarily lower this important standard that has been in place for 50 years, saved countless lives, and improved the health of so many Americans.

Thirty years after establishing these requirements, Congress again took an important step to help the FDA's fulfill its role by giving the agency the authority to collect user fees to support the review functions of the agency. The 1992 passage of the Prescription Drug User Fee Act (PDUFA) has provided essential resources to the agency to alleviate a backlog of new drug applications, and support efficient review of applications --ultimately allow Americans access to potentially life-saving new medicine.[6]

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[4] About FDA: http://www.fda.gov/AboutFDA/Transparency/Basics/ucm192695.htm Accessed 3/1/12
[5] Kefauver-Harris amendments to the 1938 Food, Drug, and Cosmetic (FD&C) Act [PL 87-781; 76 Stat. 788-89]
[6] ER Berndt, AHB Gottschalk, TJ Philipson. *Industry funding of the FDA: effects of PDUFA on approval times and withdrawal rates.* Nature Reviews Drug Discovery 4:7 (July 2005) 545-554.

The FDA is not without its critics. Recently, the FDA has been portrayed as slow and inefficient compared to other countries. Some critics have anecdotally indicated that the pathway to market approval for new medicines is more collaborative, consistent, and transparent in Europe compared to the U.S. This criticism is particularly concerning in the field of cancer, where severely ill patients have few effective treatment options. In order to explore such claims, Friends of Cancer Research conducted a study published in *Health Affairs* last summer that revealed the FDA is actually approving anti-cancer drugs in a more timely fashion than its overseas counterpart, the European Medicines Agency (EMA).[7] In fact, since 2003 to date, FDA has approved 42 new cancer medicines and EMA has approved 32. Of the 28 common approvals, all 28 were available to U.S patients first.

The intent of this research is not to conclude that one regulatory agency is approaching drug review in the best possible manner and the other is not. It is simply to provide reliable information about current trends in oncology drug review and is an example of the positive impact of the PDUFA program. In order to continue this efficient review trend, **Congress should ensure the swift passage of the PDUFA V reauthorization.**

Drug Review Authorities of the Food and Drug Administration

It should be noted that the review period prior to approval is only one component, and a relatively short one, of a multi-step process to develop new medicine. In acknowledgement of intense public health need, and due in part to new scientific methods reasonably likely to predict clinical benefit, regulations were developed to establish the Accelerated Approval mechanism for the FDA. These regulations allow for the approval of new drugs that show improvement over existing therapies to treat serious and life-threatening illnesses based upon the measure of a surrogate endpoint .[8,9] Such approvals include the requirement for additional studies to confirm the benefit predicted by the surrogate endpoint positively

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[7] Roberts S, Allen J, Sigal E. *Despite Criticism of the FDA Review Process, New Cancer Drugs Reach Patients Sooner in the United States than in Europe.* Health Affairs 30:7 (July 2011) 1375-81.

[8] 21 Code of Federal Regulations, Part 314.510

[9] 21 Code of Federal Regulations, Part 601.41

measured in the initial trials. Accelerated Approval has shown to be an important tool used by the FDA to uphold the rigorous scientific standards while facilitating access to life-saving drugs as quickly as possible. In oncology, for example, accelerated approval has been used in over a third of new cancer drug approvals since 1999 (18/53).[10]

When examining the annual trends of the recent accelerated approvals, it is noted that since 2007, the empirical number and percent of oncology drugs approved through this mechanism are less than in the period from 1999-2006, despite the overall number of new cancer drugs remaining relatively similar. The reasons for this are not fully known, and may be reflective of a variety of issues relating to the sponsors as well as the FDA.

In order to optimize this tool as a means to provide rapid access, while upholding the essential standards of FDA, **Congress should enhance Accelerated Approval to ensure that it is applied consistently, efficiently, and effectively across all therapeutic areas.** This is not to suggest in any way that the previously described standards of safety and efficacy should be adjusted or compromised, but rather to examine additional opportunities in which Accelerated Approval is the optimal approach to promote patient health based up a demonstrated improvement to a clinical endpoint.

Another mechanism that was created in the original PDUFA is Priority Review. Drugs applications that are granted Priority Review have a goal application review time that is four months shorter than the standard review goal time. For new cancer drugs since 1999, Priority Review has been granted in the vast majority of cases (77%, 41/53).[10] Of these Priority Review drugs the reduced review time goal has been met 56% of the time (23/41).

In 1997, the Food and Drug Administration Modernization Act (FDAMA) was passed and again amended Federal Food Drug and Cosmetic Act to include a new designation of Fast Track Products.[11] This

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[10] Hematology/Oncology (Cancer) Approvals & Safety Notifications: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm Accessed 3/2/12
[11] Food and Drug Administration Modernization Act of 2007 (P.L. 105-115); Section 506 (21 U.S.C. 356)

mechanism is also designed to make new promising new products available to patients without compromising existing standards of safety and efficacy. The Fast Track program is available to products intended to treat a serious and life-threatening illness, and conveys advantages such as additional meetings with FDA following designation as a Fast Track product, as well as the ability to submit clinical trial data that is part of the new drug application as it is developed, also referred to as "rolling submissions." Fast Track designation has been given to 64% (34/53) of new cancer drugs since 1999.[10]

While each of these three mechanisms have, in many cases, improved new drug review and approvals, there still remains a need to do better. While the FDA is certainly not the cause of this, additional tools could help the agency be part of the solution.

In the late 1980's another health epidemic was occurring in the form of HIV/AIDS. In 1992, due to new advancements in science and the ability to quantify and measure a surrogate endpoint, Congress gave FDA the tool to approve a drug using this scientifically advanced approach. Today, due to on-going advancements in science, the paradigm of new drug development is again beginning to shift. Much like FDA was given additional tools to address the changing scientific landscape in 1992 and 1997, an updated mechanism is needed to respond to the advancement of science today. This will continue to ensure that the most promising, novel drugs are able to reach the patients most in need.

Expedited Development of Breakthrough Products

With the expansion of knowledge about the biological basis of complex disease, new therapies are being developed that are targeted to unique molecular changes known to "drive" a disease. These new, "targeted therapies" allow selection of patients highly likely to respond to the new treatment. For these new treatments (or combinations) that show major clinical activity and significant improvement over currently-available treatment early in the new drug's development, the traditional multi-phase, sequential development approach may not be appropriate, particularly if existing treatment options have limited efficacy.

Currently, there are no clear guidelines to expedite subsequent studies that would generate the needed evidence on safety and effectiveness as efficiently as possible, and minimize the number of patients who would need to be assigned to the standard of care control. Strategies to address this challenge were discussed as part of a multi-stakeholder conference, co-hosted by Friends of Cancer Research and the Engelberg Center for Health Care Reform at Brookings, which brought together leadership from FDA, NCI, industry and advocacy.

In order to address this issue, **Congress should enact legislation that would designate a new compound that shows substantial clinical activity in early phase trials as a Breakthrough Product**. Upon designation, the sponsor, working closely with FDA, would develop trial designs to abbreviate or combine traditional phases of development. This would shorten the pathway to approval and avoid giving larger numbers of patients a potentially harmful or ineffective drug as part of a control arm, while maintaining current safety and efficacy standards.

There are a number of expedited development paths that a breakthrough product could follow. First, for diseases or disease subgroups where the natural history or the underlying disease mechanism is well understood, and the early observed treatment effect appears to have a major effect on disease course, a single arm study can be rapidly expanded at the optimal phase 2 dose to improve confidence in the estimate of the treatment effect, and to evaluate safety. If a major treatment effect continues to be seen, and safety is acceptable, the drug could be approved under either accelerated or traditional approval, depending upon the type of endpoint used in the trials. This may require post-market confirmatory trials in order to minimize the number of patients on a control arm if the only method of post-market confirmation is determined to be a randomized study.

Another scenario would involve initiating a randomized controlled phase 2 trial (with the potential for cross-over available to patients with progressive disease on the standard arm) when a large treatment effect is seen in phase 1, with the intent of generating adequate data on safety and effectiveness for

drug approval at the trial conclusion. Such a trial would be smaller and the initial interim analysis should be performed relatively early in the accrual process. This could be an accelerated or traditional approval depending on the endpoints used.[12]

The establishment of this new designation would help FDA respond to highly innovative new medicine quickly and consistently across the agency, as well as to communicate and encourage drug developers to pursue trial designs that are able to show potential benefit early in development.

Conclusion

Accelerated Approval, Fast Track, and Priority Review mechanisms play an important role in advancing new products and therapies and have shown, over time, to be an extremely important tools to get patients access to new medicine, all while upholding the essential and rigorous standards of the FDA. While this standard should not be compromised, the FDA should be given the ability to respond to cutting-edge science and the most promising new therapies. As part of the discussion regarding the reauthorization of PDUFA V congress should explore the prospect of new and/or enhanced tools to bolster FDA's ability to get drugs to market sooner and safer. An enhanced accelerated approval mechanism and the Breakthrough Product designation will allow FDA to take rapid and decisive action in these situations and optimize the path to approval for potentially life-saving new drugs and improve the medicines that are available to patients.

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[12] Friends of Cancer Research and Engelberg Center for Health Care Reform at Brookings 2011 Conference on Clinical Cancer Research: Conference Issue Brief: http://www.focr.org/images/stories/pdf/panel4final11411.pdf Accessed 3/3/12

About Friends of Cancer Research

Friends of Cancer Research (*Friends*) is a cancer research think tank and advocacy organization based in Washington, DC. *Friends* is a leader in developing partnerships and advocating for policies that will get treatments and therapies to patients in the safest and quickest way possible. Working with federal health agencies, congressional leadership, academic research centers and private sector industry, *Friends* continues to create innovative educational, policy, and scientific approaches to improve health outcomes and cancer care. www.focr.org

For more information please contact: Ryan Hohman, Director, Communications & Policy, Friends of Cancer Research at rhohman@focr.org or 202.944.6708

Mr. PITTS. The Chair thanks the gentleman.

The ranking member and I have consulted. The last time we did this, we missed a vote, so we had better break at this point. We will recess and come back to the panel as soon as the last vote of the series is over. The subcommittee stands in recess.

[Recess.]

Mr. PITTS. Time of recess having expired, we will reconvene, and the Chair recognizes Dr. Eisenstein for 5 minutes for an opening statement.

STATEMENT OF BARRY I. EISENSTEIN

Mr. EISENSTEIN. Chairman Pitts, Ranking Member Pallone and members of the subcommittee, thank you for the opportunity to testify today on the urgent need to spur greater innovation and accelerate the development of new antibiotics to combat the threat of drug-resistant pathogens. I am Dr. Barry Eisenstein, Senior Vice President of Scientific Affairs, Cubist Pharmaceuticals, a company focused on the research and commercialization of antibiotics. Headquartered in Lexington, Massachusetts, we currently market Cubicin, a first-line intravenous antibiotic for the treatment of methicillin-resistant staphylococcus aureus, better known as MRSA.

Mr. Chairman, on behalf of patients and health care experts alike, I wish to commend the subcommittee for holding this hearing and for the leadership of Congressmen Gingrey and Green and others for the introduction of the Generating Antibiotic Incentives Now, or GAIN Act of 2011. The bipartisan GAIN Act would directly promote the research and commercialization of new drugs and diagnostics against resistant pathogens. It offers our best hope to stimulate American innovation, particularly within small and mid-market companies, and strengthen the hand of clinicians and scientists in the fight against drug-resistant pathogens both here and abroad.

Annually, at least 1.7 million Americans acquire a bacterial infection in the hospital and nearly 100,000 of them die, and we have heard the heartbreaking stories. A young high school football player loses his life to a bathe with MRSA, the woman who just had mastectomy surgery acquires a resistant post-op infection and goes into kidney failure. ICU patients in American hospitals and our troops in the Middle East alike are suffering untreatable Acinetobacter infections at alarming rates, referred to earlier as Iraqibacter. Two years ago, the U.S. Air Force testified on the challenging epidemic of multi-drug-resistant infections that has resulted in a shortage of safe and effective antibiotics.

Just as antimicrobial resistance is rising, we are faced with a disturbing and dangerous lack of new antibiotic drugs, particularly against Gram-negative bacteria. The Pew Charitable Trust warns us that the antibiotic pipeline is dwindling and a global crisis looms. This threatens much of modern medicine because antibiotics are crucial from surgical recovery to cancer treatment. As Dr. William Evans, the CEO of St. Jude's Children's Research Hospital noted, "We don't want to find ourselves in a situation in which we have been able to save a child's life after cancer diagnosis only to lose them to an untreatable multi-drug-resistant infection.

The antibiotic pipeline is running dry because antibiotics uniquely are wasting assets. Bacteria evolve so quickly that the development of resistance is inevitable. Thus, each new antibiotic has only a finite lifespan. Appropriate stewardship is an important component of antibiotic use. That said by itself doesn't increase the supply of new compounds. Because antibiotics are used for acute conditions and for a short period, much of the biopharmaceutical industry does not invest in antimicrobial development and has instead turned its efforts to products aimed at more chronic diseases.

The GAIN Act is targeted at precisely this problem. By building on current law and extending the new drug exclusivities created by the 1984 Hatch-Waxman Amendments only for urgently needed antibiotics, it would dramatically improve the prospects for tracking new investments for the development and approval of new antibiotics so needed by our patients. The act would send a powerful signal to scientists and investors exploring new molecules and forming new companies as well as to large established biopharmaceutical companies that Congress recognizes the unique challenge in this area and is opening the door to new innovation, new investigations and greater investor interest. The enhanced exclusivity for antibiotics as well as the straightforward designation of qualified infectious disease products is based on what Dr. Janet Woodcock of the FDA recently described as the wildly successful Orphan Drug Act.

Mr. Chairman, this committee has a unique opportunity to take timely action against a serious public health threat. The market failure that has strained our pipeline of important new antibiotics remains. I urge the members of the subcommittee to move the GAIN Act through committee and enact it into law during this 112th Congress.

Thank you for the opportunity to testify today. I look forward to your questions.

[The prepared statement of Mr. Eisenstein follows:]

Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
Hearing on
"FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development, and Downstream Pharmaceutical Supply Chain"
Written Testimony of
Barry I. Eisenstein, M.D.
Senior Vice President, Scientific Affairs
Cubist Pharmaceuticals
March 8, 2012

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, thank you for the opportunity to testify on the urgent need to spur greater innovation and accelerate the development of new therapeutics to combat the threat of antimicrobial resistant bacterial infections.

Introduction

I am Dr. Barry Eisenstein, Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals. Cubist is a biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products – especially antibiotics -- that address critical needs in the acute care environment. Headquartered in Lexington, Massachusetts, we currently market CUBICIN® (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides. CUBICIN received FDA approval in 2003 for the treatment of complicated skin and skin structure infections caused by certain susceptible strains of Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). CUBICIN is also approved in the U.S. for the treatment of *S. aureus* bloodstream infections (bacteremia), and is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial. In the wake of a highly successful launch

of CUBICIN, the company has a growing pipeline that includes two antibiotics for difficult to treat infections planned for Phase 3 clinical trials in 2012 – one for *Clostridium difficile* and one for serious Gram-negative infections, including those caused by multi-drug resistant *Pseudomonas aeruginosa.*

As Senior Vice President of Scientific Affairs, I am responsible for leading the efforts at Cubist to understand the medical needs best answered by CUBICIN, and other antibiotics we are developing, interacting with leading scientists and health care providers in the United States and elsewhere, and advising our scientific staff regarding infectious diseases, particularly those due to resistant bacteria. I am trained in internal medicine, infectious diseases, and microbiology. I have been a hospital epidemiologist, chief of an Infectious Diseases division, chair of an academic department of microbiology and immunology, the leader of infectious diseases discovery and clinical development at a major pharmaceutical company, and am presently, in addition to my job at Cubist, Clinical Professor of Medicine at Harvard Medical School, where I teach. I hold or have held leadership positions with the Infectious Diseases Society of America, the National Foundation for Infectious Diseases, and the American Society for Microbiology, and am currently an editor of the journal, Antimicrobial Agents and Chemotherapy. I am also a member of the Foundation for the National Institutes of Health, Biomarkers Consortium. I have been studying antibiotic resistance and treating patients with infectious diseases for over three decades, have edited major textbooks, and published over 100 scholarly articles in the field.

I. Congress Has Crafted Consensus Legislation to Help Combat Antimicrobial Resistance.

On behalf of patients, infectious disease specialists, nurses, scientists, and public health experts who work in clinical settings, academia and industry nationwide, I wish to commend this Subcommittee, led by Chairman Pitts and Mr. Pallone, Chairman Upton and Mr. Waxman, for working so actively and patiently to better prepare the United States against the serious public health threat of antimicrobial resistant organisms. Also, I commend Congressmen Gingrey and

Green for introducing the GAIN Act along with the many members of this committee who are co-sponsors, especially our home state congressman, Representative Markey.

For more than six years, since before the last reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2007, you have systematically convened hearings, heard expert testimony, participated in multilateral meetings, and pursued intensive dialogues with patient groups, public health and specialty societies, and innovative industry, in order to develop and introduce focused, well-reasoned legislation that could greatly accelerate the discovery of new antimicrobials. This legislation has the support of many major national organizations engaged in the struggle to combat antimicrobial resistance.

Just a few years ago, it was not at all certain that Congress and the infectious disease community would respond to this crisis as quickly and capably as it has. Two years ago, I testified before this Subcommittee that "We [were] approaching a 'crisis point' with antimicrobial resistance and the lack of new therapies against Gram positive bacteria such as 'staph' and Gram negative bacteria such as *Acinetobacter.*" Four years ago, I testified to your Senate colleagues on the Health, Education, Labor and Pensions (HELP) Committee that "we must implement effective measures to combat antimicrobial resistance."

Today, I am happy to return to this Subcommittee, as it considers enacting critically important legislation to combat antimicrobial resistance, and report that your concern over this public health crisis, and your desire to take timely, targeted action to increase innovation, now constitute a national consensus that is broadly shared by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Food and Drug Administration (FDA); the Infectious Disease Society of America (IDSA) ; independent authorities such as The Pew Charitable Trusts and Extending the Cure; governors of life science-leading States like Massachusetts; 35 military and veterans associations; St. Jude's

Children's Research Hospital; and the innovative biopharmaceutical companies like Cubist.

Together over the past several years, we have confirmed that the risks to public health at home and abroad are great and the gaps in our medical preparedness and our therapeutic options are not only substantial, but also growing with every passing month. Together, we have identified the market failure that has hollowed out antimicrobial innovation, and we have tailored policies that could serve as concrete solutions and make a critical difference in the lives of millions of Americans annually.

Mr. Chairman, the result of this sustained collaboration is H.R.2182, the Generating Antibiotic Incentives Now, or GAIN, Act of 2011. This consensus, bipartisan public health measure – introduced by Dr. Gingrey and his colleagues I mentioned, and cosponsored by many of the present members of this Subcommittee – would extend Hatch-Waxman exclusivity only for select "qualified infectious disease products" that would significantly improve our therapeutic and clinical abilities to combat infections caused by resistant pathogens. The GAIN Act would, in addition, assure that novel antibiotics receive priority review or fast track status under the Food and Drug Administration's (FDA) existing authority. The bill also provides for additional exclusivity for "qualified infectious disease products" developed in conjunction with a companion diagnostic test. Finally, the Act calls for the FDA to revise its guidelines for clinical trials of antibiotic drugs to reflect the latest developments in science and clinical knowledge.

These clear and impactful policies would directly promote the research and commercialization of new drugs and diagnostics against resistant pathogens. Taken together, the provisions in the GAIN Act offer our best hope to stimulate American innovation and strengthen the hand of clinicians and scientists in the fight against antimicrobial resistance both here and abroad.

II. Antimicrobial Resistance is a National Public Health Threat

As the Subcommittee is aware, during the last several decades, the prevalence of antimicrobial resistant organisms in U.S. hospitals and medical centers has increased. According to 2002 data from the Centers for Disease Control and Prevention (CDC), more than 1.7 million people acquire bacterial infections in U.S. hospitals each year, and 99,000 die as a result. CDC estimates that up to 70 percent of those bacterial infections are resistant to at least one drug, at a cost of approximately $5 billion annually.

The IDSA estimates that the treatment of resistant pathogens costs more than $20 billion annually to our health care system and result in Americans spending more than 8 million additional days in the hospital. A study published in the *Journal of the American Medical Association* extrapolated data from nine U.S. communities to estimate that there were 94,360 invasive MRSA infections alone in the U.S. in 2005 which resulted in 18,650 deaths—to say nothing of the prevalence of other drug resistant pathogens.

Intensive care patients in American hospitals and our troops in the Middle East conflicts alike are suffering untreatable *Acinetobacter* infections at alarming rates. Two years ago, the House Armed Services Oversight Subcommittee received testimony from the U.S. Air Force on the "challenging epidemic" of "multi-drug resistant ... infections [that] has resulted in a shortage of safe and effective antibiotics." Then - Chairman Vic Snyder of the House Armed Services Committee, Oversight and Investigations Subcommittee, stated ". . . [T]he problem could get worse in the next several years, because there are few new antibiotic treatments expected from the drug research pipeline."[1] You are also well aware of the disturbing rates of MRSA and the emergence of vancomycin-resistant enterococci (VRE) increasingly leave infectious disease doctors with few, if any, effective therapies for certain strains of bacterial infection. Just as antimicrobial

[1] Press Release, Fighting Superbugs: Oversight and Investigations Subcommittee Holds Hearing on Military's Efforts to Prevent Outbreaks of Multidrug-Resistant Infections in Military Hospitals; United States House of Representatives Armed Services Committee Democrats. September 30, 2010

resistance is rising, we are faced with a disturbing and dangerous lack of new antibiotic drugs, particularly against Gram negative bacteria.

III. Multiple Solutions Are Being Applied to Antimicrobial Resistance But At This Time, None Can Generate New Antibiotics

Mr. Chairman, there is no question that limiting the spread of serious infections, as well as improving practitioners' use of antibiotics, are critically important to combating resistant pathogens. Infection prevention and control programs, the use of clinical practice guidelines, and basic steps like proper hygiene in health care settings, can all have a substantial impact on limiting the emergence of resistance and the number of patients infected. Improving the quality, timeliness, and usefulness of infectious disease surveillance is also of great importance, as is the need to sustain our Federal investment in biomedical research through the National Institutes of Health (NIH).

Over the past decade, Congress and the infectious disease community have cooperated to develop, enact, implement, and assess many new policies and Federal initiatives to combat resistant pathogens. For example:

- The federal Interagency Task Force on Antimicrobial Resistance in focused federal R&D funding was authorized in 1999 after a hearing on the dangers of antimicrobial resistance.
- In 2002, Congress further broadened this funding authority in the aftermath of the deliberate biological attacks against the Capitol and in New York, New Jersey and Florida.
- In the 2007 PDUFA reauthorization, at our encouragement, this Subcommittee authored provisions directing FDA to update its regulatory guidance and revise critical clinical breakpoints for antibiotics, as well as to determine whether the Orphan Drug Act could be made available to promote development of new antimicrobial drugs.
- In 2009, the Affordable Care Act included provisions to improve the quality of inpatient care against hospital-acquired infections, created a

short-term incentive called the Qualifying Therapeutic Discovery Project Tax Credit, and provided CDC and States with additional infection control funding.

In short, these policies are important and necessary, but they will not and simply cannot, fill our medicine cabinets. They cannot close the dangerous gaps in our therapeutic options: our efforts to improve the education of clinicians, better manage the prescribing of antibiotics, reduce health-care acquired infections, and conduct more basic research can only accomplish so much. Just as our medicine cabinets are becoming empty, so too our policy toolbox has been emptied.

IV. GAIN Act Would Target Market Failures, Accelerate Antimicrobial Innovation

As a result, Mr. Chairman, The Pew Charitable Trusts warns us that "[t]he antibiotic pipeline is dwindling, and a global crisis looms." That is why the GAIN Act is so urgently needed. The Act builds on previous Federal and congressional enactments, by specifically targeting the market failures and policy gaps that have led us to this crisis point.

The antibiotic pipeline is running dry because antibiotics, uniquely, are "wasting assets." Bacteria evolve so quickly that the development of resistance is inevitable. Thus, each new antibiotic only has a finite lifespan. Appropriate stewardship is an important component of antibiotic use, as its primary goal is to optimize clinical outcomes while minimizing the unintended consequences of antimicrobial use (e.g. toxicity, selection of pathogenetic organisms, emergence of resistance). But it paradoxically reduces the commercial returns necessary to induce the investment, research and clinical trials that lead to new, approved antibiotics. In addition, antibiotics are used for acute conditions and for a short period. Consequently, much of the biopharmaceutical industry does not invest in antimicrobial development and has instead turned its efforts to products and more chronic diseases with the potential for greater commercial returns on investment.

The GAIN Act is targeted at precisely this problem. By extending the new drug exclusivities created by the 1984 Hatch-Waxman Amendments, it would dramatically improve the prospects for attracting new investments for the development and approval of new antibiotics so needed by our patients. The Act would send a powerful signal to scientists and investors exploring new molecules and forming new companies, as well as to large, established biopharmaceutical companies, that Congress recognizes the unique commercial challenges in this area, and is opening the door to new innovation, new investigations, and greater investor interest.

As this Subcommittee knows, the GAIN Act deliberately builds on current law and the foundation of the Hatch-Waxman Amendments to support innovation. The enhanced exclusivity for antibiotics, as well as the straightforward designation of "qualified infectious disease products", is based upon what Dr. Janet Woodcock of the FDA recently described as the "wildly successful"[2] Orphan Drug Act, which has led to more than 2,150 orphan drug designations and 358 new, approved therapies for rare diseases and disorders. . ."

We believe implementation of the GAIN Act is certain to succeed because the Act envisions early consultations between companies and the FDA based on the orphan drug model, and a designation that is based on clear criteria that target the most serious infections. Finally, the review of FDA's guidances, and the assurance of priority review or fast track status on the basis of FDA's current authorities, promise to further expedite the development and approval of new antibiotics.

Conclusion

Mr. Chairman, this Subcommittee has a unique opportunity to take timely action against a serious public health threat. The market failure that has

[2] Janet Woodcock, June 9, 2010 Hearing in Energy and Commerce; Transcript p. 65. Available at: http://democrats.energycommerce.house.gov/documents/20100609/transcript.06.09.2010.he.pdf

drained our pipeline of important new antibiotics remains. As Congress acts to reauthorize the Prescription Drug User Fee Act in a timely and bipartisan manner before the end of this fiscal year, so too should it enact the GAIN Act. I urge the Members of this Subcommittee to move the GAIN Act through Committee and enact it into law during this 112th Congress.

Thank you for the opportunity to testify today. I look forward to your questions.

Mr. PITTS. Thank you, Dr. Eisenstein.

Dr. Powers, you are recognized for 5 minutes for an opening statement.

STATEMENT OF JOHN H. POWERS

Mr. POWERS. Good afternoon. Thank you for inviting me to testify today. My name is John Powers, and I am a practicing infectious disease and internal medicine physician and a medical researcher who actively cares for patients. I was a scientist at FDA for almost a decade, and while there, I was one of the co-chairs of the Interagency Task Force on Antimicrobial Resistance.

I would like to share with you today my perspectives as a clinician, researcher, and having been a patient myself on appropriately developing incentives for antibiotics where there is the greatest need. My remarks are my own views, and I am not representing any agency or organization, but I am here speaking on behalf of the patients for whom I care. Several patients and consumer and public health groups have expressed the same views as I will present here today.

Government intervention is needed to spur antibiotic development because antibiotics are less profitable for drug companies than other therapeutic areas resulting in decreased investment. The Generating Antibiotic Incentives Now, or GAIN bill, provides those incentives to develop new antibiotics.

In any policymaking, as in science, one must first outline the problem, then come up with potential solutions while minimizing unintended consequences, implement that policy, and then measure whether it has its intended effects. The problem of serious diseases for which there are no effective therapies has been well outlined. The question now is, how best can GAIN address these problems. If the public to make an investment on new antibiotics, the public should get something of measurable value in return while not worsening the problem of antibiotic resistance. Several changes to GAIN might help it focus to best address public health needs while limiting potential adverse consequences.

First, GAIN should focus on patients and their diseases rather than organisms. I have never had a patient tell me their E. coli hurts or that their Klebsiella is killing them. Patients present with disease syndromes like pneumonia, and I have certainly heard enough people in this room coughing today to show that symptoms are a problem.

The human body contains more bacterial than human DNA, and organisms do not cause problems for patients until they cause disease. In fact, the word "pathogen" implies pathology and disease. Any list of organisms in the bill would be quickly outdated and hard for FDA to implement. In addition, FDA regulations appropriately point out that drugs are approved for recognized diseases or conditions, and organisms are neither. Use of antibiotics to eliminate organisms in the absence of disease would paradoxically increase antibiotic resistance.

Second, GAIN should focus on the treatment of serious and life-threatening diseases where lack of safe and effective therapies results in death or serious disability. Antibiotic resistance in the test tube has little effect on patients who would recover without anti-

biotics but it is inappropriate use in these settings that has worsened antibiotic resistance. Despite efforts by CDC, FDA, and others, a substantial portion of antibiotic prescriptions are still not warranted, provide no benefits to patients, and cause the problem of antibiotic resistance we are trying to control.

Third, there should be valid scientific evidence based on FDA's standard of substantial evidence from adequate and well-controlled trials that these drugs actually unmet medical needs. In a 1979 landmark Supreme Court case, Thurgood Marshall pointed out that people with terminal diseases should not receive less protection under the law from unsafe and ineffective drugs than persons with curable diseases. Test tube and animal studies are helpful in choosing drugs to study in people, but people are not rodents. The complexity of the human body is totally humbling. Three-fourths of antibiotics submitted to FDA for review with promising test tube and animal studies ultimately fail to show safety and efficacy in human disease. Approving antibiotics today hoping for some future promise makes no sense as resistance is inevitable with all antibiotics, sometimes occurring before the drug is even marketed. There is no guarantee that a drug approved today will address resistance tomorrow. In a study from Boston, almost half of antibiotics approved since 1980 have disappeared from the market, either because of safety and efficacy issues or because of poor sales because they did not address public health needs. Therefore, numbers of drugs approved is not a measure of public health benefits.

Fourth, we need new tools to evaluate antibiotics that will make trials more efficient and less expensive for companies to perform. Determining who needs and who does not need antibiotics and developing better outcome measures to evaluate directly how patients feel and function are urgently needed so we can get the valid evidence we need to know if the drugs actually meet unmet medical needs.

Fifth and finally, any incentives should go hand and hand with programs for appropriate stewardship of antibiotics. For any scarce resource, conservation should accompany increased production. Unfortunately, we as physicians have been only moderately successful at policing ourselves to appropriately use antibiotics but greater efforts are underway. FDA should be given the authority to develop strategies to evaluate and ensure appropriate antibiotics where they are most needed and to minimize antibiotic resistance. An HHS-level internal group to address issues related to antibiotic resistance would help strengthen ongoing efforts of the interagency task force.

Focusing the GAIN bill on the five ways I have just outlined will result in addressing the goals it sets out to achieve: developing new and safe antibiotics with an appropriate evidence base to positively affect patients' lives while simultaneously limiting antibiotic resistance.

Thank you very much.

[The prepared statement of Mr. Powers follows:]

Incentives for Addressing Unmet Needs in Antibiotic Development:

Focusing the GAIN Bill for Patients in Greatest Need

John H. Powers, MD

Associate Professor of Medicine

George Washington University School of Medicine

United States House of Representatives

Committee on Energy and Commerce Committee

Subcommittee on Health

March 08, 2012

"FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development, and Downstream Pharmaceutical Supply Chain"

Good morning. Thank you for inviting me to testify. I am a practicing infectious disease and internal medicine physician and a medical researcher who actively cares for patients. I was a scientist at FDA for almost a decade and while there I was one of the co-chairs of the Inter-agency Task Force on Antimicrobial Resistance. I would like to share with you today my perspectives as a clinician, researcher and patient myself on appropriately developing incentives for antibiotics where there is the greatest need. My remarks are my own views and I am not representing any agency or organization, but I am here speaking on behalf of the patients for whom I care. Several consumer and public health groups and advocates have expressed the same views I will present here today.

Government intervention is needed to spur antibiotic development because antimicrobials are less profitable for drug companies than other therapeutic areas, resulting in decreased investment in new antibiotic development. The Get Antibiotic Incentives Now or GAIN bill provides incentives to develop new antibiotics.

In any policy making as in science, one must first outline the problem, come up with potential solutions while minimizing unintended consequences, implement the policy and then measure whether it has had its intended effects. The problem of serious diseases for which there are no effective therapies has been well-outlined. The question is how best can GAIN address these problems? If the public is to make an investment on new antibiotics the public should get something of measurable value in return while not worsening the problem.

Several changes to GAIN might help it focus to best address public health needs while limiting potential adverse consequences.

First, GAIN should focus on patients and diseases, not organisms. I have never had a patient tell me their *E. coli* hurts or their *Klebsiella* is killing them. Patients present with disease syndromes like pneumonia. The human body contains more bacterial than human DNA. Organisms do not cause problems for patients until they cause disease. Any list of organisms in the bill would be quickly outdated. In addition, FDA regulations appropriately point out that drugs are approved for "recognized diseases or conditions" and organisms are neither. Use of antibiotics to eliminate organisms in the absence of disease would paradoxically increase antibiotic resistance.

Second, GAIN should focus on the treatment of serious and life-threatening diseases where lack of safe and effective therapies result in death or serious disability. Antibiotic resistance in the test tube has little effect on patient outcomes in self-resolving disease, but it is inappropriate use in these settings that has worsened antibiotic resistance. Despite efforts by CDC, FDA and others a substantial proportion of antibiotic prescriptions are not warranted, provide no benefit to patients and cause the problem we are trying to control.

Third, there should be valid scientific evidence based on FDA's standard of substantial evidence from adequate and well-controlled trials that drugs meet unmet medical needs. In 1979 in a landmark Supreme Court case Thurgood Marshall pointed out that people

with terminal disease should not receive less protection under the law from unsafe and ineffective drugs than persons with curable diseases. Test tube and animal studies are helpful in choosing drugs to study in people, people are not rodents. Three fourths of antibiotics submitted to FDA for review with promising test tube data and animal studies ultimately fail to show safety and efficacy in human disease. Approving antibiotics today hoping for some future promise makes no sense as resistance is inevitable with all antibiotics, sometimes occurring before a drug is even marketed. There is no guarantee that a drug approved today will address resistance tomorrow. Almost half of antibiotics approve since 1980 have disappeared from the market, either because of safety and efficacy issues or because of poor sales because they did not address public health needs, therefore number of drugs approved is not a measure of the public health benefits.

Fourth, we need new tools to evaluate antibiotics that will make trials more efficient. Determining who needs antibiotics and developing better outcome measures to evaluate how patients feel and function are urgently needed so we can get the valid evidence we need to know if drugs meet the claims made for them.

Fifth and finally, any incentives should go hand in hand with programs for appropriate stewardship of antibiotics. For any scarce resource, conservation should accompany increased production. Unfortunately, we as physicians have been only moderately successful at policing ourselves to appropriately use antibiotics. FDA should be given the authority to develop strategies to evaluate and ensure appropriate use of antibiotic where they are most needed and minimize antibiotic resistance. An HHS level internal group to

address issues related to antibiotic resistance would help strengthen ongoing efforts of the Inter-Agency Task Force.

Focusing the GAIN bill in the five ways I have just outlined will result in addressing the goal it sets out to achieve – developing new safe and effective drugs with an appropriate evidence base to positively affect patients' lives while limiting antibiotic resistance.

Mr. PITTS. Thank you, Dr. Powers.

Mr. Walsh, you are recognized for 5 minutes.

STATEMENT OF MICHAEL WALSH

Mr. WALSH. Thank you. Mr. Chairman, Mr. Ranking Member, thank you for inviting me to testify today. My name is Mike Walsh. I am President of LifeGas. This is part of Linde North America. We are headquartered in New Jersey. We have about 4,500 employees in the United States.

I am here today to testify on behalf of the Compressed Gas Association, of which we are a member. CGA represents companies engaged in the manufacture and distribution of compressed gases including medical gases.

The Compressed Gas Association was founded in 1913 and currently has more than 120 member companies. CGA serves as a safety standard-setting organization for the medical gas industry. The medical gas companies in our coalition employ about 21,000 employees and have around 4,500 locations, half of which are small businesses. I personally entered into this industry, the medical gas industry, as a small business owner.

Linde and other members of the Compressed Gas Association provide medical gases that are used by doctors, primarily for respiratory care. You can find our products in hospitals, clinics, doctors' offices and in homes across the country.

On behalf of the CGA, I want to offer my thanks to Congressman Leonard Lance and Chris Murphy for introducing the Medical Gas Safety Act. Your leadership role in this issue has been pivotal. I also want to thank Chairman Pitts and Ranking Member Pallone for your willingness to address these issues in the very important bill you are working on now. Naturally, I also want to thank Chairman Upton and Ranking Member Waxman of the full committee as well.

Medical gases, like oxygen, are used by medical practitioners as prescription drugs every day. We have over a million patients using it in a variety of conditions. Medical oxygen has been used for more than a century. Medical gases were in use for decades before the FDA was created and a New Drug Application process was initiated. And here is the really key point. Medical gases have a long, long history of safe and effective use. The most common ones are derived today, things we are breathing today. These common medical gases are a unique class of drug products that are different from traditional pharmaceuticals in a lot of ways. We have different properties than pharmaceutical drugs: we have a different delivery method, we have a different manufacturing process, we have a different type of container that holds the product. Medical gas manufacturers make no medical claims for medical gases, which is very different for traditional prescription drugs.

However, the FDA currently regulates medical gases with the same regulatory system as traditional pharmaceuticals. This has created significant and growing regulatory issues. These practical issues create uncertainty and drive up compliance costs for our industry. Medical gases need a separate regulatory system that takes into account these unique characteristics.

The Medical Gas Safety Act addresses a number of critical regulatory issues facing the medical gas industry. It establishes an appropriate approval process for medical gases. It requires the creation of separate regulations for medical gases. It ensures that FDA fees do not disproportionately impact medical gas manufacturers, many of whom are small businesses. This legislation will create regulatory certainty for our industry. It will ensure that patients in the medical community have access to these lifesaving products. It will remove current uncertainty regarding the Federal regulations of medical gases for Federal and State inspectors.

The FDA has recognized the unique nature of medical gases for a very long time. Until now, the FDA has generally used its enforcement discretion not to require medical gases to go through the New Drug Application process. Recently, the FDA began the Unapproved Drugs Initiative, which is intended to eliminate all unapproved drugs from the marketplace including medical gases. If the Unapproved Drugs Initiative is applied to medical gases, this would remove access for patients to gases as simple as oxygen.

Recent changes in enforcement policies related to the export of unapproved drugs have also created serious challenges for our industry. Also, the regulatory system in place for medical gases does not take into account the unique characteristics of medical gases. In response to concerns raised by the Compressed Gas Association, the FDA stated in 1976 in the preamble to the original Current Good Manufacturing Practices rulemaking that they intend to develop separate regulations for medical gases. No such regulations have been developed.

This legislation will provide a clear, targeted regulatory structure for medical gases, creating a process for medical gases to become approved drugs and establishing specific regulations for medical gases which will reduce uncertainty, improve compliance and improve safety in what is already a very safe industry.

I applaud all of you again for your willingness to address these important and longstanding regulatory issues. Thanks again on behalf of the CGA for the opportunity to testify.

[The prepared statement of Mr. Walsh follows:]

Testimony of Michael Walsh
President of LifeGas
Before the Health Subcommittee of the House Energy and Commerce Committee
"FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain"
March 8, 2012

Mr. Chairman, Mr. Ranking Member, thank you for inviting me to testify today. My name is Mike Walsh. I am President of LifeGas, which is part of Linde North America. Linde is headquartered in New Jersey and has about 4,500 employees in the United States. I am here today testifying on behalf of the Compressed Gas Association, of which Linde is a member. CGA represents companies engaged in the manufacture and distribution of compressed gases, including medical gases.

The Compressed Gas Association was founded in 1913 and currently has more than 120 member companies. CGA serves as the safety standard setting organization for the medical gas industry. The medical gas companies in our coalition employ about 21,000 people in 4,500 different locations, half of which are small businesses. I personally entered into the medical gas industry as a small businessman.

Linde and other members of the Compressed Gas Association provide medical gases that are used by doctors primarily for respiratory care. You will find our products in hospitals, clinics, emergency centers, long-term care settings, dentist offices and in homes through homecare companies across the country.

On behalf of the CGA, I want to offer my thanks to Congressmen Leonard Lance and Chris Murphy for introducing the Medical Gas Safety Act. Your leadership role on this issue has been pivotal. I also want to thank Chairman Pitts and Ranking Member Pallone for your willingness to address these issues in the very important bill you are working on.

Naturally, I also want to thank Chairman Upton and Ranking Member Waxman of the full committee as well.

Medical gases like oxygen, helium, and nitrogen are used by medical practitioners as prescription drugs every day by over a million patients for a variety of conditions. Medical oxygen has been used for more than a century. Medical gases were in use for decades before FDA was created and the New Drug Application process was initiated

Here is the key point: Medical gases have a long history of safe and effective use. The most common ones are derived from the air that we breathe every day. These common medical gases are a unique class of drug products that are different from traditional pharmaceuticals in a number of ways:

- They have different properties than traditional prescription drugs;
- They have different delivery methods;
- They are manufactured differently;
- Their containers and labeling are different; and
- Medical gas manufacturers make no medical claims for the vast majority of medical gases, which is very different from traditional prescription drugs.

However, FDA currently regulates medical gases with the same regulatory system as traditional pharmaceuticals. This has created significant and growing regulatory issues. These practical issues create uncertainty and drive up compliance costs for our industry. Medical gases need a separate regulatory system that takes into account their unique characteristics.

The Medical Gas Safety Act addresses a number of critical regulatory issues facing the medical gas industry. It establishes an appropriate approval process for medical gases. It

requires the creation of separate regulations for medical gases. It ensures that FDA fees do not disproportionately impact medical gas manufacturers, many of whom are small businesses. This legislation will create regulatory certainty for our industry. It will ensure that patients and the medical community have access to these life saving products. It will remove the current ambiguity regarding the federal regulation of medical gases for federal and state inspectors.

The FDA has recognized the unique nature of medical gases for a long time. Until now, FDA has generally used its "enforcement discretion" not to require medical gases to go through the new drug application process. Recently, the FDA began the "Unapproved Drugs Initiative," which is intended to eliminate all "unapproved drugs" from the marketplace, including medical gases. If the Unapproved Drug Initiative is applied to medical gases, this would remove access for patients to medical gases like Oxygen.

Recent changes in enforcement policies related to the export of unapproved drugs have also created serious challenges for the industry. The FDA has started requiring medical gases being exported to be labeled as "unapproved." This has caused some customers to cancel or delay orders from U.S. companies, even though these products are recognized as safe and effective. As a result, these customers may be buying their products from other countries where medical gases are not labeled as "unapproved." The Medical Gas Safety Act would address this issue and establish an appropriate approval process for medical gases.

Similarly, the regulatory system in place for medical gases does not take into account the unique characteristics of medical gases. In response to concerns raised by the Compressed Gas Association, the FDA stated in 1976 in the preamble to the original Current Good Manufacturing Practices rulemaking that they intend to develop separate regulations for medical gases. No such regulations have been developed. This lack of

specific regulations for medical gases has resulted in decades of unwritten enforcement discretion for federal and state regulators and uncertainty for the regulated industry.

For example, FDA has told the industry it will not enforce the expiration date requirement for medical gases. However federal and state inspectors often try to enforce expiration date requirements on medical gases, which never expire. For instance, Oxygen is an element of the periodic table. By its basic properties it will never expire. However current FDA regulations require all drugs, including medical gases like Oxygen, to have an expiration date.

The Medical Gas Safety Act would create an appropriate approval process for medical gases that do not have FDA approval, but have been widely used and accepted as safe and effective. It would set up a regulatory framework for such medical gases that would address issues like labeling requirements and good manufacturing practice requirements. These issues are very important. It would create an advisory committee to give expert advice to the FDA. They could share with FDA the vast library of appropriate safety standards that have been created by CGA. And it would ensure that fees for medical gases are proportional to the actual regulatory costs for a group of products that historically have a low risk profile.

This legislation will provide a clear, targeted regulatory structure for medical gases. Creating a process for medical gases to become approved drugs and establishing specific regulations for medical gases will reduce uncertainty, improve compliance and improve safety in what is already a very safe industry. It will benefit doctors, patients, distributors, manufacturers and even regulators. It will ensure safety and continued availability of extremely important products used every day. I applaud all of you again for your willingness to address these important and longstanding regulatory issues.

Thank you again, on behalf of CGA, for the opportunity to testify. I will be glad to answer any questions you might have.

Mr. PITTS. Thank you. Thank you for your testimony. The Chair thanks the panel for being patient waiting while the members voted. We will now begin questioning, and I will recognize myself for 5 minutes for that purpose.

Dr. Maraganore, in your testimony, you cite the success of FDA's Accelerated Approval pathway for HIV and AIDS and cancer treatments but indicate the Accelerated Approval framework has done little to help expedite treatments for rare diseases. Can you elaborate on why the accelerated pathway has not led to gains in the rare-disease space that you would all like to see?

Mr. MARAGANORE. Yes. I think it really speaks back to the comments that Dr. Woodcock in terms of the clarity around the utility and the usefulness of the Accelerated Approval process for diseases outside of cancer and HIV/AIDS, and clearly what I think is being proposed in Congressmen Stearns' and Towns' proposal is a way of significantly enhancing and modernizing our understanding of Accelerated Approval to the point where it will be used more frequently, I would expect, for the purposes of rare or orphan diseases where there significant unmet medical need and certainly an important desire I think for patients and physicians to have access to medicines faster.

Mr. PITTS. Now, some experts believe that FDA is seeking to limit the use of Accelerated Approval for cancer drugs. Is this the case? Rather than narrowing the use of Accelerated Approval in cancer, shouldn't we be looking for ways to expand it, and what should Congress to prevent FDA from limiting its use?

Mr. MARAGANORE. I think there has been some concern around potential changes within the FDA's views on how Accelerated Approval would be used in cancer based on some hearings that were held about this time last year. You know, clearly, the FDA has used this approach for cancer-based medicines. We believe that the FDA will continue to do so. I think our desire is really to see it expanded and clarified as a system while very importantly maintaining the safety and efficacy standards that exist today for the approval of medicines.

Mr. PITTS. And how would the FAST Act incentivize research and development of innovative therapies and treatments for serious diseases?

Mr. MARAGANORE. Well, clearly, the ability of having a clear and established framework whereby medicines in the context of very serious unmet medical needs can be approved through an Accelerated Approval pathway would certainly encourage the investment that is needed to ultimately bring these types of products to the marketplace. Clearly, innovative medicines are increasingly being discovered by, you know, young companies like ours, of which there are many in this country, in a very vibrant industry, but this industry as been challenged by the increasing time it takes to get drugs to the marketplace and the increasing costs, and Accelerated Approval in the context of very serious unmet medical needs would provide a framework for getting drugs to patients faster in a way that would be more acceptable to the investors that have to put capital at risk to ultimately bring these products to market.

Mr. PITTS. Thank you.

Dr. Eisenstein, while the threat of antibiotic drug resistance is a looming public health crisis, the drug development pipeline has not kept pace with this threat. What can we do to turn this around?

Mr. EISENSTEIN. Thank you for your question, Mr. Chairman. I believe that the GAIN Act as presently formulated provides us with precisely the right tools to provide the incentives needed. To cite Dr. Woodcock's earlier testimony: "We need economic incentives beyond the regulatory ones for these bad bugs." Industry needs a clear pathway to the market. I could not have said that better myself, and when one looks at the enormous success of the Orphan Drug Act that was enacted in 1983, the Office of the Inspector General in reviewing that in 2001 declared, A, that it was extraordinarily successful in enabling at the time over 200 new drugs. We are now over 350 new drugs through the Orphan Drug Act. But I would say equally importantly, they pointed out that the increased market exclusivity was the most important determinant of the success of that program. So I believe we have everything we need in the GAIN Act as it presently written.

Mr. PITTS. Thank you.

Mr. Walsh, I understand that FDA regulation has caused problems for many in the medical gas business. Many of these are small businesses. Can you explain how and why FDA regulation has caused these problems?

Mr. WALSH. Yes. Thank you. I was one of those small business owners, and when I had started this business, we were under the guidelines of a grandfathered product, and if I would have known today what I had known back then, I would not have started this business. We went on and created through our employees a great organization with nearly 1,000 employees but we are marketing, distributing and selling an unapproved drug, and so you are asking to invest in that and then the regulations if we were forced to go under a strict pharmaceutical standard would be too expensive for the small companies to follow.

Mr. PITTS. My time is expired. The Chair recognizes the ranking member for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask Dr. Allen a question and then I wanted to ask Dr. Powers a question. Let me start with Dr. Allen. I think we all agree that FDA needs to be able to be flexible in determining approval requirements and we have heard from Dr. Woodcock and your testimony, there is ample evidence that FDA does in fact use its authority in a flexible manner, and that has enabled FDA to get important drugs through the regulatory process in a timely manner and some circumstances based on quite limited data. That being said, I recognize there can be advantages to clarifying and improving some of FDA's authorities to facilitate its use of Accelerated Approval pathways, and I think the pathway you propose for breakthrough therapies deserves serious consideration as does the pathway put forward in the FAST Act by Representatives Stearns and Towns and the Special Population Limited Use pathway proposed by IDSA in its submitted testimony.

My main concern, Dr. Allen, is about any proposal to help speed new therapies to market is that it doesn't lower the safety or effec-

tiveness standards by which FDA approves new medicines. Now, I know you mentioned that you don't want to—I think you actually said in your testimony "I don't want to lower the safety or effectiveness standards." But I just wanted you to basically expand on that a little. Do you agree that whatever improvements we make—well, you said that you don't think they should lower the safety and effectiveness standards but if you would spend a little time just giving me some more information on that.

Mr. ALLEN. Well, thank you for the question. First of all, I absolutely agree that the current standards of safety and efficacy that have been in place for decades need to continue to be upheld, first and foremost. I think the difference in what we are proposing here through the idea of a breakthrough designation, it is important to distinguish that Accelerated Approval is an approval mechanism where the breakthrough is a designation or a process-oriented question, and what we are seeing, and I am most familiar with oncology, of course, is that there are new drugs being developed that are highly targeted and being used in select populations where they achieve the greatest benefit and the lowest amount of toxicity, and in those cases, the traditional development plan of a phase I followed by a phase II followed by a phase III trial may not always be appropriate, and there may be ways to expedite that, and we have worked with several expert groups including the National Cancer Institute, the FDA, the Brookings Institute and others to look at those strategies, and while it was mentioned that there may not need to be new law, I think that the 1.5 million Americans that will hear the words "you have cancer" this year would appreciate looking at all policies that will help expedite promising new therapies to them quickly.

Mr. PALLONE. Well, thank you.

Now, Dr. Powers, one of the things you alluded to is the issue of making sure the use of antibiotics is targeted to infections for which they are actually useful and making sure that the patients actually have those infections. One feature currently included in the GAIN Act is the availability of 6 months of additional exclusivity for an antibiotic if its manufacturer develops a companion diagnostic test to use with a new antibiotic. I understand that in order to really accomplish the goal of directing new antibiotics to the right patients, a test would have to help identify where in the body an infection is, what kind of bacteria is causing it, and should suggest or ensure that the antibiotic in question is an appropriate treatment for the infection. Did I get that right? Can you tell me more about whether you think it is possible to develop tests that accomplish this and how to make sure that we are not giving additional incentives for tests that may not help us conserve precious antibiotics?

Mr. POWERS. That is correct, and I think it gets back to the issue of disease versus just harboring an organism in your body. So if we were to develop diagnostics that merely tell you that you have an organism on your nose, that wouldn't help us if we then treat all those people when that treatment wouldn't help. On the other hand, if we specifically develop diagnostics to show that people have a disease, that would be more helpful, and through the current 510(k) process that FDA utilizes for medical devices, you don't

necessarily need to show anything other than you can detect an organism. So we would need to go beyond that and actually have helpful information, not only for clinical trials so we can enroll the right people but also those could be useful in practice as to who to direct antibiotics to and who not to treat.

Mr. PALLONE. But you think it is possible to develop tests that accomplish this, right?

Mr. POWERS. I think the technology is there, and I think that is why it is helpful to develop incentives that would help people to do this.

Mr. PALLONE. Thank you.

Mr. Chairman, if I could ask—I know we gave this to you a little while ago, ask unanimous consent to include in the record the statement of the Infectious Diseases Society of America?

Mr. PITTS. Without objection, so ordered.

Mr. PALLONE. Thank you.

[The information follows:]

Statement of the Infectious Diseases Society of America (IDSA)

Promoting Anti-Infective Development and Antimicrobial Stewardship through the U.S. Food and Drug Administration Prescription Drug User Fee Act (PDUFA) Reauthorization

Before the House Committee on Energy and Commerce's Subcommittee on Health

March 8, 2012

Infectious Diseases Society of America's (IDSA) Statement
Promoting Anti-Infective Development and Antimicrobial Stewardship
through the U.S. Food and Drug Administration
Prescription Drug User Fee Act (PDUFA) Reauthorization
Before the House Committee on Energy and Commerce
Subcommittee on Health
March 8, 2012

The Infectious Diseases Society of America (IDSA) appreciates this opportunity to submit testimony for the record in support of the House Energy and Commerce Committee Health Subcommittee's efforts to enact strong incentives to spur new anti-infective research and development (R&D) and promote antimicrobial stewardship (i.e., the appropriate use of these critically important drugs) as part of the U.S. Food and Drug Administration (FDA) Prescription Drug User Fee Act (PDUFA) reauthorization legislation. This is an opportunity that we cannot afford to miss. IDSA thanks the Subcommittee Chairman and Ranking Member for including a focus on antibiotics in today's hearing and for including IDSA's statement in the hearing record. The Society also commends Representatives Gingrey and Green, and all of the bipartisan cosponsors of the Generating Antibiotic Incentives Now (GAIN) Act for their leadership in beginning to craft solutions to the complex and most urgent problems of antimicrobial resistance and the dry antibiotic R&D pipeline.

IDSA represents nearly 10,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections. Of relevance to today's hearing, our members also care for an increasing number of patients with serious and life-threatening antimicrobial-resistant infections—infections against which we have frighteningly few effective therapeutics available. To call attention to this growing public health crisis, IDSA issued a landmark report in 2004 to launch our Bad Bugs, No Drugs advocacy campaign. To broaden the scope of this critical effort to include other countries and to provide a measurable goal for progress and success, in 2010, IDSA launched "The 10 x '20 Initiative," which calls for a global commitment to develop 10 new systemic antibiotics by the year 2020. In January 2012, a group of 50 organizations representing patients, health care providers, health systems, veterans, women's health, children's health, seniors, and other key stakeholders wrote to House and Senate leaders in support of The 10 x '20 Initiative and urged Congress to address the serious and growing problems of antimicrobial resistance and the dry antibiotic R&D pipeline as part of PDUFA. A copy of their letter is attached for the hearing record.

IDSA's statement today will briefly summarize the synergistic crises of rising rates of antibiotic resistance and waning approvals of new antibiotics. IDSA's goal is to represent the best interests of patients and health care professionals by recommending, within the context of the GAIN Act and PDUFA, public policy strategies to reverse antibiotics' decline and save lives. To this end, in addition to focusing on ways to reduce the economic disincentives that have persisted leading to a market failure in antibiotic R&D, IDSA today also is raising for the Subcommittee's consideration a new FDA approval mechanism, tentatively called **"Special Population Limited Medical Use (SPLMU) Drugs"** (see page 5) which we believe could be a potential game changer for the most urgently needed anti-infective products. After reviewing IDSA's statement,

should you be interested in learning more about the problem of antimicrobial resistance as well as additional solutions, please review IDSA's recent policy paper titled "Combating Antimicrobial Resistance: Policy Recommendations to Save Lives," and other important resources, available on The 10 x '20 Initiative website at: http://www.idsociety.org/10x20.

I. Antimicrobial Resistance: A Growing Public Health Crisis

In 2000, Nobel Laureate Dr. Joshua Lederberg wrote in the journal *Science* that "the future of humanity and microbes will likely evolve as episodes … of our wits versus their genes." In only 12 years since Dr. Lederberg wrote these prescient words, the world has witnessed an enormous expansion of infections resistant to antibacterial agents ("antibiotics"). For example, antibiotic-resistant Gram-negative bacteria (GNB) have spread widely through U.S. and global health care systems. Increasingly they have become resistant to all antibiotics available for treatment—i.e., pan-drug resistant (PDR). A wide array of patients are particularly vulnerable to GNB infections, including individuals recovering from surgery or trauma, cystic fibrosis patients, burn victims, cancer patients undergoing chemotherapy, and transplant recipients. These dangerous and often deadly bacteria can infect the skin, brain, bones, joints, and urinary tract and may cause abdominal infections, pneumonia, meningitis, and bacteremia. Examples of PDR GNB organisms include *Acinetobacter baumannii* (which is threatening soldiers returning from Afghanistan as well as patients throughout the U.S. and the world), carbapenemase-producing *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa.* Such infections kill an astonishingly high percentage of infected patients (e.g., greater than 50%-60% of patients with infection in the blood, greater than 40%-50% of patients with lung infection, etc.) despite any available treatment. Furthermore, extended-spectrum beta lactamase (ESBL)-producing Enterobacteriaceae (e.g., *Escherichia coli [E. coli]* and *Enterobacter spp.*), which often are resistant to all orally administered antibiotics, have spread through health care systems and more recently into communities. Such infections make it impossible to treat common urinary tract or abdominal infections with antibiotic pills, requiring hospitalization for intravenous antibiotic therapy. Most recently, a new antibiotic resistance mechanism (New Delhi metallo-β-lactamase 1 or NDM-1) emerged in India and spread to communities in the United States, United Kingdom, and elsewhere. NDM-1, *E. coli,* and several other GNB strains are resistant to all antibiotics except perhaps tigecycline or colistin, and increasingly to these drugs as well.

In October 2011, 562 infectious diseases physicians who are members of IDSA's Emerging Infections Network (EIN) responded to a survey about antibacterial-resistant infections. More than half (63%) of respondents reported caring for a patient with an infection resistant to all available antibacterial drugs in the prior year. 64% of respondents reported using colistin during the past year to treat a patient suffering from these infections. Colistin is an antibiotic that was discovered in the 1940s, but was found to be highly toxic having great potential to cause kidney and other organ damage. For this reason, colistin's use was all but abandoned in the 1950s—until, in the wake of the growing tide of antimicrobial resistance over the last decade, it has become the drug of last resort despite the fact that it has well-known toxicity, its effectiveness has been questioned, and resistance to the drug has increased. With so few therapeutic options, physicians are grasping at straws.

Collectively, highly problematic antibiotic-resistant organisms are summarized by the ESKAPE mnemonic: ***Enterococcus***, ***Staphylococcus***, ***Klebsiella***, ***Acinetobacter***, ***Pseudomonas***, and **ESBL** (*Enterobacter* and *E. coli*). ESKAPE indicates that these bacteria have developed defenses that permit them to escape the actions of available, effective therapies. The ESKAPE pathogens are currently the most important causes of the antibiotic resistance crisis in the U.S. and other developed countries. Such pathogens also are spreading through developing countries, which already are experiencing significant public health problems from extreme drug-resistant (XDR) or PDR *Mycobacterium tuberculosis* (TB). Collectively, disease caused by the ESKAPE pathogens, TB, and other highly problematic antibiotic-resistant bacterial pathogens, including hypervirulent and fluoroquinolone-resistant *Clostridium difficile*, and multi-drug resistant (MDR) *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*, result in enormous morbidity, mortality, and health care expense in the U.S. and throughout the world.

According to the U.S. Centers for Disease Control and Prevention (CDC), in 2006, just one organism alone, methicillin-resistant *Staphylococcus aureus* (MRSA), killed more Americans (~19,000) than emphysema, HIV/AIDS, Parkinson's disease, and homicide combined. Almost 2 million Americans per year develop hospital-acquired infections (HAIs), resulting in 99,000 deaths, the vast majority of which are due to antibiotic-resistant pathogens. Indeed, two common HAIs alone (sepsis and pneumonia) killed nearly 50,000 Americans and cost the U.S. health care system more than $8 billion in 2006. In a recent survey, approximately half of patients in more than 1,000 intensive care units in 75 countries suffered from an infection, and these infected patients had twice the risk of dying in the hospital as uninfected patients. Based on studies of the costs of infections caused by antibiotic-resistant pathogens versus antibiotic-susceptible pathogens, the annual costs to the U.S. health care system and society of antibiotic-resistant infections is $21 billion and $34 billion, respectively, and more than 8 million additional hospital days. Antimicrobial resistance was recently recognized as one of the greatest threats to human health on the planet. For that reason, the World Health Organization (WHO) proclaimed antimicrobial resistance the focus of World Health Day (April 7) 2011.

Clostridium difficile (C. diff), the top cause of infectious diarrhea in hospitals, is a bacterium that has become increasingly common in health care facilities across the U.S. Though *C. diff* is frighteningly common in hospitals, 75% of *C. diff* infections now start in places such as nursing homes or doctor's offices. *C. diff* is increasingly resistant to antibiotics, and an epidemic strain is highly resistant to a very common class of antibiotics known as fluoroquinolones. Inappropriate antibiotic use is significantly contributing to this growing problem. A recent study found that *C. diff* will lengthen a hospital stay by an average of 6 days for infected patients. Not only is this drug-resistant infection placing a serious burden on our health care system, it also is costing patients their lives. *C. diff* infections kill 14,000 Americans each year, and deaths caused by this pathogen increased 400% between 2000 and 2007.

Finally, the problem of antimicrobial resistance is not specific to bacteria—medically important fungi (e.g., Candida spp.), viruses (e.g., HIV, influenza), and parasites (e.g., malaria) also develop antimicrobial resistance.

II. The Dry Antibiotic Pipeline

Ironically, as the number of patients succumbing to antibiotic-resistant infections rises, the number of new antibiotics in development is plummeting. Since IDSA's 2009 report on the status of the antibacterial R&D pipeline[1], only two new antibiotics have been approved in the U.S. and the number of new antibiotics approved annually continues to decline. A 2011 study found nine intravenous compounds active against resistant GNB in clinical development (phase II or phase III studies). Only two of these compounds demonstrated a novel mechanism of action, and none of the candidate drugs was active against all pan-resistant GNB. These findings continue to underscore the need for antibiotic incentives and a feasible approval pathway to advance desperately needed new antibiotics. Moreover, in 1990, there were nearly 20 pharmaceutical companies with large antibiotic R&D programs. Today, few remain. Not only does the tumbling private investment in antibiotics R&D jeopardize the development and availability of sorely needed new antibiotics in the United States, it also drains indispensable jobs and intellectual capital as companies seek to do business in countries with more favorable economic and regulatory climates.

Antibiotic R&D poses unique scientific, regulatory, and economic challenges, which often makes antibiotic R&D riskier than R&D for other types of drugs. One company reports that over a 10-year period, it took 72 lead candidate antibiotic compounds in the early discovery phase to yield one FDA-approved product; other drug types only took 15 leads to yield an FDA approval. Antibiotics also provide less financial reward for companies as they are used for a short duration (i.e., often 7 to 14 days), typically are priced low, and are encouraged to be held in reserve to protect against the development of drug resistance, rather than used widely as most other drugs are once approved.

Antibiotics play a unique role in medicine and are extremely valuable to society. The appropriate use of these drugs, when they are available, helps stop the spread of serious and often deadly bacterial infections from one person to another. If the antibiotic crisis is not addressed soon, we face a future that resembles the days before these miracle drugs were developed, one in which people died of common infections, and where many medical interventions that we take for granted—including care for premature infants, surgery, chemotherapy, organ transplantation, and even dentistry for some patients (like those with hip replacements, etc.)—become impossible.

Strengthened investment in new antimicrobial agents also is essential for U.S. national security. An October 2011 Bio-Response Report Card issued by the Bipartisan WMD Terrorism Research Center—chaired by former Senators Bob Graham and Jim Talent—concluded that a terrorist armed with an antibiotic-resistant pathogen could produce a large-scale event with "catastrophic consequences," resulting in a "potentially uncontrollable number of illnesses and/or deaths," "civil and political unrest in the affected region," and a "global economic impact."

If Congress fails to incentivize antibiotic R&D, this crisis will deepen, more lives will be lost, and more health care dollars will be needlessly spent.

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[1]Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1-12.

III. New Antimicrobials: Providing Regulatory Pathways to Approval

During a recent policy meeting, representatives from the few pharmaceutical companies still investing in antibiotic R&D said they plan to focus their future efforts on European, Asian, and Latin American markets and not on the United States. The primary reason for this shift: the regulatory environment. For more than a decade, FDA's antibacterial human drug review process has been fraught with uncertainty that has shaken the foundation of the nation's antibacterial pharmaceutical industry. FDA has failed to fully appreciate, prioritize, and address the unique challenges facing antibiotic development, and the lack of a clear antibiotic approval pathway, coupled with economic disincentives, has brought antibiotic development to its knees. Companies need consistency, feasibility, predictability, and timeliness in order to make investment decisions. FDA has made it difficult, if not impossible, for companies to plan new investments in the antibiotics area first by throwing out existing rules without having new guidelines available to replace them and more recently by proposing new requirements that have been deemed infeasible both by industry and by independent infectious diseases physician experts. While FDA must periodically update the rules for approving new drugs to keep pace with the advancing science, they also must provide an approval pathway that works.

FDA has an essential role to play in ensuring that Americans have access to safe and effective drugs. But, in so doing, the agency must ensure that the risks associated with approving new products are appropriately balanced against the products' benefits to patients and to society. To date, when it comes to antibiotics, and particularly antibiotics needed to treat the most serious bacterial infections, FDA's risk benefit equation has been out of balance. The urgent need for new anti-infective therapies to treat patients with serious or life-threatening infections who lack satisfactory therapeutic options, usually because of resistance to available therapies, requires new thinking and action.

Special Population Limited Medical Use Approval Mechanism

To begin to address the most urgent needs in anti-infective R&D, IDSA is proposing, for the Subcommittee's consideration and as a critical addition to the GAIN Act, a new FDA approval mechanism, tentatively called **"Special Population Limited Medical Use (SPLMU) Drugs." The mechanism would provide an important new approval pathway option for companies interested in and able to develop drugs to treat patients with the most serious infections where few or no therapeutic options exist.** Using the mechanism, a drug sponsor would seek a designation for and the FDA would approve the designation of eligible SPLMU drugs. The drug's safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials than traditionally required. In return, the drug would be narrowly indicated for use in a small, specific population of patients for whom the benefits of the drug have been shown to outweigh the risks. The designation, a description of the population in which the drug is indicated, the rationale for limiting use to that population, and a logo signifying the designation would appear in the drug's label and labeling. **The SPLMU mechanism would effectively limit marketing of the anti-infective to the population in which a positive benefit-risk ratio has been established and, importantly, it would foster prudent use of anti-infective drugs to slow the rate at which resistance to the drugs develops.**

The fundamental purpose of the SPLMU drug development program is to enable drug development targeting serious infections that lack available, satisfactory therapeutic options—very much like the Orphan Drug Program, under which these products do not fit, according to FDA officials. IDSA believes this new mechanism could bring critically needed innovation to the anti-infective pipelines and help focus development on areas of particular unmet medical need. Furthermore, the concept likely will have potential benefits for other serious diseases and conditions as well (e.g., obesity). IDSA is aware of at least seven companies with urgently needed antibiotics in their portfolios; establishment of this new drug pathway could immediately help these companies bring new antibiotics to the ever-increasing number of patients who desperately need them. **IDSA has discussed the SPLMU Drug mechanism with leaders at FDA and in industry, and there seems to be strong interest in exploring the concept's merits.** In fact, one company has indicated to IDSA a strong interest in pursuing the SPLMU mechanism for their urgently needed antibiotic, if the pathway can be established quickly enough to accommodate their development cycle. **We encourage Subcommittee members and staff to explore the concept with Dr. Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, and individual companies for their assessment, during and following today's Subcommittee hearing.**

What is the problem the SPLMU mechanism is intended to address and how will it work?
Many diseases, such as those caused by bacterial, viral, and fungal infections, have a broad spectrum of severity. The SPLMU mechanism is intended to address the needs of a special population of patients with serious manifestations of such diseases who lack satisfactory treatments. In caring for such severely ill patients with limited treatment options, health care providers, regulators, and society can tolerate a greater degree of uncertainty about overall risk associated with a drug than can be tolerated in patients with milder manifestations of the disease, or those who have more satisfactory therapeutic options. Using the SPLMU mechanism, FDA will have an important role to play in ensuring that the appropriate conditions of use are described in a drug's labeling, but will not have a role in authorizing or prohibiting use of approved products within the practice of medicine. Instead, through the use of this new high profile designation, logo, and labeling, FDA will be providing notice to the health care community, including health care facilities, practitioners, and payors, as well as to patients, that these products carry less precise estimates of risk because of smaller pivotal clinical trials and, hence their use must be limited to the indicated population.

To further help assure the drugs are used appropriately and encourage use according to the labeled indication, the drug's sponsor would submit a general post-market surveillance plan to FDA prior to the drug's approval outlining how the sponsor plans to monitor drug utilization. The company also would submit all promotional materials related to the product during the preapproval period and, following approval, to FDA at least 30 days (or another timeframe determined by FDA to be appropriate) before dissemination of these materials.

We anticipate that a SPLMU designation that targets an extremely small segment of the population, will, like an Orphan Drug Act designation, markedly decrease costs of development and simultaneously increase the price of these critically-needed new drugs, making investment in their R&D more attractive to pharmaceutical companies. The same assumption of increased pricing will mean payors too will play a more active role ensuring the drugs are used as indicated

and that confirmatory follow-up tests (i.e., culturing specimens) are being conducted to validate a drug's appropriate use. As a result, the development of drug resistance to the SPLMU antibiotic should occur more slowly.

How will the SPRMU make it easier for companies to achieve approval for the critically needed new drugs addressing specific unmet medical need?
Traditionally the FDA has required conduct of two, large, phase III non-inferiority clinical trials (in addition to numerous phase I and II trials) to support approval of a new antibiotic (as for other drugs). Such trials are very expensive (e.g., >$50 million-$100 million) and take a long time to complete. Thus, companies will only conduct such studies when the perceived potential market size of a new drug is very large, encompassing both susceptible and resistant bacteria causing common infections. It is not feasible for drugs that treat specific, highly resistant pathogens to be developed using clinical trials conducted at this scale.

The requirement for large-scale clinical trials to support approval is based on the need to provide a very clear understanding of the relative risks and benefits of a new drug to treat common illnesses. In particular, if there are already other therapeutic options available to treat a specific disease that has favorable risk-benefit ratios, the tolerance for safety risks is substantially lower for newly approved drugs to treat the same disease. Thus, drugs developed to treat these diseases generally go through a comprehensive evaluation of risks in the broad disease population likely to use the drug (e.g., to rule out a risk of a low frequency, serious adverse event that would not be acceptable in patients with such disease). These large trials add significant costs and often delay or discourage development, thus depriving those with serious manifestations of the disease and limited treatment options (a population in whom the benefit may justify increased uncertainty about the risk) of viable therapeutic options.

For serious diseases for which few if any acceptable treatments are available, the tolerability for risk is much higher. As an example, before the first HIV drug was approved, even highly toxic drugs were appropriately deemed approvable, because the infection itself caused nearly a 100% mortality rate. As more and more new anti-HIV drugs became approved, the death rate from HIV infection plummeted, and there was an increasingly safe group of antiretroviral drugs already on the market. As such, the tolerability for risk for each successively approved new agent became lower and lower, appropriately so.

Similar to the early years of HIV drug development, the risk-benefit ratio of approved SPLMU drugs will be quite different than for less serious diseases and/or diseases for which numerous available therapies exist. The SPLMU concept enables clinical development programs that are more limited than a traditional development program that would result in use of the drug in a broad population suffering from less serious infections. Also likely to be of great interest to companies, we anticipate, based on our discussions with FDA leaders, that this mechanism could be used to facilitate development of an antibacterial to treat serious infectious diseases due to the same resistant pathogen at multiple disease sites—a critical public health need. Clinical data could be pooled from infections caused by the targeted bacterial pathogen at several different body sites (e.g., pneumonia, bloodstream infection, intra-abdominal infection). Moreover, these data, in combination with data from in vitro studies, animal models of infection (with pharmacokinetic and pharmacodynamic data), human pharmacokinetic and pharmacodynamic

data, and important microbiologic information about the mechanism of action of the new drug and the mechanisms of resistance, could support approval for use in serious infections due to the resistant pathogen. This mechanism also could be considered for developing therapies for multi-drug-resistant tuberculosis (MDR-TD)—a critical public health issue because current therapeutic regimens are not very effective.

In addition, the SPLMU Drug designation could be temporary or permanent. If the drug sponsor later went through a traditional study route for an indication for the anti-infective the limited use designation could be removed.

How else will the SPLMU approach help to address antimicrobial resistance?
By helping to limit prescription of drugs approved by the SPLMU mechanism to patients who fall within the special population indicated on the FDA-approved label, the mechanism would protect individual patients outside of the special population from exposure to drugs that may pose an uncertain risk. Furthermore, the SPLMU mechanism also would serve a broader public health purpose for anti-infective therapies as it could be used to help deter development of resistance to important drugs by encouraging their use to only those patients with a highly resistant, target pathogen. Because companies may only market drugs according to their FDA approved indication, the SPLMU mechanism would be a potent means of limiting advertisement/marketing of the drug for a narrow, appropriate use. Such focused marketing would help prevent inappropriate, broader use of such life-saving medications, thereby slowing the spread of resistance and prolonging the drugs' useful lives.

In addition, the SPLMU mechanism will help to enforce the understanding that anti-infective drugs provide an important societal benefit that necessitates the need for greater societal responsibility. We believe this new approval mechanism will promote the development and implementation of antimicrobial stewardship programs in health care facilities across the United States—a priority for IDSA and the infectious diseases community in general. (See additional discussion about antimicrobial stewardship below.) And, although antibiotics typically are prescribed empirically (i.e., without culture tests being performed to confirm the diagnosis), IDSA anticipates and will help to encourage, along with the health care community and payors, that confirmatory tests are performed in patients prescribed antibiotics approved under the SPLMU mechanism so that the drug can be discontinued in patients found not to be in the indicated population.

In summary, the important benefits of the SPLMU mechanism include:

- **Creation of a new anti-infective drug approval pathway that permits a more appropriate risk-benefit ratio for serious infections and will bring lifesaving medicines to those patients most seriously in need of them.**

- **Empowering FDA to innovate the anti-infective pipeline by providing them flexibility to more rapidly approve urgently needed medicines.**

- **Rightly leaving in physicians' hands the power to oversee the use of approved products within the practice of medicine.**

- **A streamlined approval pathway that will enable pharmaceutical companies to study SPLMU drugs in far fewer patients than currently is required, more rapidly, and at significantly less cost.**

- **A likely higher valuation of these precious drugs among payors, providers, patients, and society in general.**

- **Placing the burden of protecting these drugs on those stakeholders best positioned to ensure their appropriate use (e.g., health care providers, health care systems, payors, patients).**

- **Promoting the establishment of critically needed antimicrobial stewardship programs in health care facilities across the United States.**

Institute of Medicine (IOM) Review of FDA Anti-Infective Clinical Trial Design
In addition to considering the SPLMU mechanism in the context of the GAIN Act and PDUFA, IDSA also recommends that the Subcommittee direct FDA to engage with the Institute of Medicine (IOM) in a process to review the operational feasibility of FDA's current approaches to the design of anti-infective (including antibacterial, antifungal, and influenza antiviral) drug clinical trials. The IOM could: assess the limitations and strengths of FDA's current statistical approaches; provide new perspectives on approaches to balancing public health risk vs. benefit of decisions that must be made, even in the face of incomplete or imperfect data, and applied to the evaluation of the safety and efficacy of new anti-infective drugs; and make recommendations leading to more rapid improvements in regulatory science.

Foundation for the National Institutes of Health (FNIH) Initiative
In 2010, FDA contacted the Foundation for the NIH (FNIH) Biomarkers Consortium to request its assistance in reviewing and assessing the evidence available for making regulatory decisions for some antibacterial drug clinical trials. Specifically, this initiative is an independent collaboration with academia, industry, IDSA, and others to advance development of antibacterial trial endpoints. The initial focus for this effort is skin infections and pneumonia. Congress should seek out ways to support this and similar initiatives to improve the regulatory pathway for approval of new antimicrobial drugs.

IV. Antimicrobial R&D: Removing Economic Disincentives

To fix the broken antimicrobial pipeline and stimulate the development of desperately needed new antimicrobial drugs, IDSA has long advocated that a combination of push and pull incentives will be necessary. The GAIN Act takes an important step in the right direction by providing a type of pull incentive—increased data exclusivity for new antibiotics. However, this incentive, while helpful, alone will not sufficiently raise the net present value (NPV) of antibiotics sufficiently to permit them to compete fairly against other drugs for companies' R&D investment resources. To that end, IDSA recommends the following incentives be added to the GAIN Act for inclusion in PDUFA:

Push Incentives

Public Private Collaborations
The European Union (EU), through its Innovative Medicines Initiative, is launching a new collaborative research effort focused on antibiotics for serious resistant pathogens.[2] The EU recognizes that the extent of action required to significantly impact the challenges facing the discovery and development of novel antibiotics is too great for any single entity. This new initiative will focus on the discovery and development of antibiotics targeting drug-resistant priority pathogens. IDSA applauds the EU for its leadership and urges Congress to take steps toward a similar, complementary initiative in the U.S. Even if the Subcommittee determines that the GAIN Act cannot be used to establish a public private partnership, surely the legislation can be used at least to designate a lead agency to explore the options in this arena and to report back to Congress on those options within one year. Such options should include the possibility of working jointly with the EU and other countries on a public private collaboration to address this growing global problem. Designating a lead agency to explore these options could be done at little or no cost. If we do not act, we run the risk of further eroding our competitive edge and losing valuable intellectual capital and jobs.

Other Push Incentives
While exclusivity provides value to companies once a drug is on the market, numerous economic models have indicated that push incentives (i.e., providing value early in R&D) are necessary to spur new antimicrobial development. Such incentives could include tax credits, grants, or other mechanisms of direct funding through the National Institutes of Health and the Biomedical Advanced Research and Development Authority (BARDA). While the Energy and Commerce Committee does not have jurisdiction to pursue all of these options, we encourage Committee Members to indicate their support for exploration of these proposals to colleagues on the House Ways and Means and Appropriations Committees.

Pull Incentives

Exclusivity
The increased exclusivity provided by the GAIN Act attaches to the end of existing Hatch/Waxman data exclusivity and would run concurrent with most antibiotics' existing patent terms. As such, GAIN will keep competitors off the market only in limited cases when the original drug's development period took so long that less than 10 years of patent life remains available post-approval. For the average antibiotic, 10 to 12 years of patent time typically remains post-approval. Thus, GAIN's exclusivity incentive's primary benefit will be to protect companies from patent infringement suits during the additional 5 years of exclusivity. Such an incentive may be particularly helpful for a company with potentially weak intellectual property rights.

To raise antibiotics' NPV even further and thus spur antibiotic R&D for the patients who need them, IDSA has proposed that exclusivity also must be applied at the end of all remaining

[2] http://www.imi.europa.eu/sites/default/files/uploads/documents/Future_Topics/IMI_AntimicrobialResistance_Draft20120116.pdf

exclusivity and patent time to keep competitors' drugs off the market longer. Structured in this manner, IDSA's exclusivity proposals will likely not score a cost to the federal government for the next decade or two, given the average amount of patent life typically remaining on new antibiotics at the time they are approved. Major companies, including GlaxoSmithKline (GSK) and Pfizer, agree with IDSA's assessment. To strengthen GAIN's exclusivity provision, consider the addition of (1), (2), and (3) below in descending order of priority:

(1) A period of exclusivity (e.g., 5 years) that attaches to the end of all existing exclusivity and patent periods, thereby prohibiting the approval of competitors' drug applications during the protected period. In its first 10 years (1997-2007), pediatric exclusivity has helped to generate more than 900 pediatric studies, and over 430 products have undergone labeling changes for pediatric use—demonstrating that exclusivity at the end of patent life is a model worth considering. Both GSK and Pfizer have modeled this incentive and agree that it would provide substantial additional benefit over the current GAIN exclusivity provision.

(2) An additional period of exclusivity (e.g., 3 years) that attaches at the end of all existing exclusivity and patent periods if the antibiotic is the first of a new class because, for example, the active moiety of the product achieves its therapeutic effect through a new mechanism of action or targets a site on the infectious pathogen not targeted by products previously approved. For purposes of this new provision, FDA will need to define in regulations the term "antibiotic class" as this term currently is not defined. However, many experts agree only one new class of antibiotic has been approved since the 1970s. New classes of antibiotics can provide valuable new protections against drug-resistant pathogens, and thus, creating new antibiotic classes should be a priority for GAIN.

(3) Any exclusivity period extended pursuant to the GAIN Act should be further extended by additional exclusivity (e.g., 1 year) at the end of all existing exclusivity and patent periods for each subsequent approval an antibiotic receives for treating an additional infection or pathogen where FDA deems the subsequent approval(s) address a critical unmet need. It makes sense to consider limiting this incentive, e.g., no antibiotic could receive more than three such extensions. This incentive will spur companies to conduct additional research on approved antibiotic drugs, thus, providing valuable effectiveness and safety information about how these drugs work in patients suffering these infections; without such additional studies physicians will not have access to this critical information.

V. The Scope of GAIN's Impact

To address the infections posing the greatest risk to patients (and therefore of greatest concerns to ID physicians), ensure the GAIN Act is applicable to drugs and related diagnostics that treat and detect new infectious pathogens as they emerge, and best fits the way FDA approves antibacterial drugs (currently by indication based on infection and not pathogen), IDSA agrees with others that it would be best to modify the GAIN definition of "qualified infectious disease product." We propose the following revised definition: *"an anti-infective (including antibacterial, antifungal, and influenza antiviral drugs) for human use that meets the statutory definition of a new chemical entity; is indicated for use in a serious or life-threatening*

infections; and which demonstrates the potential to address unmet medical needs for such disease or condition."

It is IDSA's understanding that Subcommittee members are considering whether to expand the scope of the GAIN Act to cover antifungal drugs. Fungi can cause serious and life-threating infections, particularly in cancer patients, HIV/AIDS patients, and the elderly. The costs of treating these infections are skyrocketing, and the morbidity and mortality associated with invasive fungal infections is extremely high. For these reasons, IDSA supports covering antifungals that treat serious and life-threatening infections in the GAIN Act and thus we include them in our proposed revised definition above.

We also have added language to cover influenza antivirals. We realize that this request is new and that Subcommittee members want to keep the GAIN Act definition narrow to address the most urgent needs. However, we want Subcommittee members to be aware that influenza antivirals are desperately needed to reduce the current high levels of influenza-associated morbidity and mortality in the United States. CDC estimates that seasonal influenza epidemics result in an average of more than 200,000 influenza-related hospitalizations and a range of approximately 3,400 to 49,000 influenza-related deaths each year in the U.S. Of particular note, there were 122 pediatric influenza-associated deaths in the U.S. last season, and the number of pediatric deaths ranges from 46 to153 each year. There also were more than 300 deaths in children from the 2009 pandemic H1N1 in the U.S. We currently have only two effective influenza antivirals available, and one of these drugs is not available to treat many types of patients, including children under the age of five. In addition, there are very real concerns that resistance is developing against these two available drugs in circulating influenza strains. New effective antiviral drugs are urgently needed to prevent severe infections and deaths among large numbers of adults and children during future seasonal outbreaks and pandemics of influenza. IDSA experts are available to discuss with Subcommittee members and staff the state of antibacterial, antifungal, and influenza antiviral drug development and the threats posed by antimicrobial resistance in all three areas.

VI. Incentives for Development of Rapid Diagnostics

Diagnostic tests are a critical part of the solution to the problems of antimicrobial resistance and R&D, and can play a critical role in detecting and identifying emerging infections as well as biothreats. Rapid, highly sensitive, point-of-care diagnostics improve physicians' ability to effectively treat patients and prescribe antibiotics in a manner consistent with antimicrobial stewardship. We need diagnostic tools to accurately identify serious, drug-resistant bacterial, fungal, and viral pathogens and, importantly, to inform the physician when the pathogen he or she is trying to treat is a virus and therefore untreatable using antibiotics. Thus, diagnostics can be extremely helpful in preserving for a longer window of time the effectiveness of approved antibiotics. Better diagnostics also reduce the costs of new anti-infective development by increasing the number of microbiologically evaluable patients in the clinical trial population. There are currently serious challenges to enrolling eligible patients in clinical trials for new antimicrobials.

Unfortunately, numerous disincentives exist that hamper the development of new diagnostic tests including the expense of collecting clinical specimens against which to validate diagnostics, difficulty in obtaining FDA approval for diagnostic tests, challenges in securing Medicare and private insurance coverage of new diagnostics, and a lack of value-based reimbursements for these tests.

A good first step toward strengthening diagnostics R&D will come from establishing a centralized specimen biorepository to house patients' clinical specimens (e.g., tissue, sputum, blood, urine) collected during clinical trials. Such a repository would strengthen infectious diseases research and critically needed diagnostics development by reducing redundancies (i.e., eliminate the need for multiple players to collect the same types of specimens numerous times), assuring that quality specimens are collected, and saving valuable time and resources. A similar Cancer Human Bio-Bank (ca-HUB) is being established by the National Cancer Institute (NCI). On this concept, the Institute of Medicine has opined that, "The broader use of high-quality, standardized repositories would speed the pace of scientific and clinical advances at a much lower expense than would be required if new clinical samples had to be collected to study each new concept." IDSA proposes that the same is true for infectious disease research, particularly related to diagnostics.

IDSA recognizes that the Subcommittee may be hesitant to include a provision in GAIN to create such a repository. However, we firmly believe this idea is worthy of consideration and therefore recommend that the GAIN Act or PDUFA direct the National Institutes of Allergy and Infectious Disease (NIAID), in conjunction with CDC, FDA, and the Assistant Secretary for Preparedness and Response (ASPR), to consult with non-government stakeholders including representatives from diagnostics and pharmaceutical companies, academia, and professional societies to explore the feasibility of creating a biorepository of prospectively collected specimens. In so doing, NIAID and the others should consider whether such a repository would lower the cost of clinical validation of, and otherwise assist with the R&D for, diagnostic tests intended to advance the treatment, detection, identification, prevention, or control of antimicrobial-resistant infections. Consideration of this idea by these agencies could be done at little to no cost. Further, NIAID also should examine the feasibility of making the biorepository self-sustaining by establishing a program under which non-governmental entities could pay a fee for access to each human biological specimen, including costs related to the overall maintenance and operation of the biorepository.

VII. Antimicrobial Stewardship and Appropriate Use

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration. The major objectives of antimicrobial stewardship are to achieve best clinical outcomes related to antimicrobial use while minimizing adverse events and the emergence of antimicrobial resistance. Antimicrobial stewardship also may reduce excessive costs attributable to suboptimal antimicrobial use. As the Subcommittee considers providing greater federal support to incentivize new antibiotic R&D, it is equally important to safeguard that investment with policies

to ensure that antibiotics do not rapidly become obsolete due to the overuse that drives resistance.

Next week IDSA, the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) will release a policy statement on antimicrobial stewardship that will put forth our joint position on antimicrobial stewardship. However, IDSA's fundamental position already has been made public. We recommend that all health care facilities, including hospitals, long-term care facilities, long-term acute care facilities, ambulatory surgical centers, and dialysis centers be required to develop and implement an antimicrobial stewardship plan as a condition of participation in Medicare and Medicaid. IDSA recognizes that the Subcommittee does not have sole jurisdiction over Medicare, but we encourage you to consider ways to promote the appropriate use of antibiotics through the GAIN Act. Specifically, IDSA recommends that the following language regarding antimicrobial stewardship be added to the GAIN Act:

"The Secretary shall, in cooperation with CDC and CMS, promote measurement of antibiotic usage across all health care settings and support adoption and implementation of comprehensive antimicrobial stewardship programs across all health care settings to promote the appropriate use of antibiotics. Flexibility in program requirements must be allowed based on facility size and type."

Moreover, GAIN's definition of "qualified infectious disease product" could be further modified to require a drug sponsor to provide to FDA during the drug review process a plan for educating health care providers in all health care settings on the drug's appropriate use and to reinforce precautions to reduce the risk of resistance.

VIII. Conclusion

In conclusion, IDSA thanks the Subcommittee once again for its leadership and focus on antimicrobial resistance and the dry anti-infective pipeline. These are complex, multi-faceted problems that require a combination of policy solutions, including regulatory improvements, push and pull economic incentives, new diagnostics tests, and establishment of antimicrobial stewardship programs in each health care facility to ensure the continued development and long-term utility of antimicrobial drugs. IDSA looks forward to continuing to work with the Subcommittee to enact the strongest possible package of solutions through the GAIN Act and PDUFA.

ATTACHMENT

February 22, 2012

The Honorable John Boehner
Speaker of the House of Representatives
1011 Longworth House Office Building
Washington, DC 20515

The Honorable Nancy Pelosi
House Minority Leader
235 Cannon House Office Building
Washington, DC 20515

The Honorable Eric Cantor
House Majority Leader
303 Cannon House Office Building
Washington, DC 20515

The Honorable Steny Hoyer
House Minority Whip
1705 Longworth House Office Building
Washington, DC 20515

The Honorable Fred Upton
Chairman of the House Energy and Commerce Committee
2183 Rayburn House Office Building
Washington, DC 20515

The Honorable Henry Waxman
Ranking Member, House Energy and Commerce Committee
2204 Rayburn House Office Building
Washington, DC 20515

The Honorable Joe Pitts
Chairman of the Health Subcommittee
420 Cannon House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member of the Health Subcommittee
237 Cannon House Office Building
Washington, DC 20515

Dear U.S. House Leaders:

We, the undersigned organizations representing patients, health care providers, health systems, veterans, women's health, children's health, seniors, and other key stakeholders urge you to address the serious and growing problems of antimicrobial resistance and the dry pipeline for antibiotic research and development (R&D) in upcoming Food and Drug Administration (FDA) user fee legislation. A growing number of patients are suffering from and succumbing to antimicrobial-resistant infections, because we have too few, and in some cases no, antibiotics to treat them. Ironically, as the number of patients succumbing to resistant infections rises, the number of new antibiotics in development is plummeting.

If Congress does not enact strong solutions, we face a future that resembles the days before these miracle drugs were developed, one in which people died of common infections, and where many medical interventions that we take for granted—including care for premature infants, surgery, cancer chemotherapy, organ transplantation, and even dentistry for some patients—become impossible. Antimicrobial resistance also is placing a significant burden on our health care system—costing over $20 billion annually in health care costs according to one study. To save patients' lives, we support U.S. efforts that strive to achieve the laudable goal of approving ten new systemic antibiotics by 2020. Read more about ***The 10 x '20 initiative*** (http://www.idsociety.org/10x20) on the Infectious Diseases Society of America's website.

In 1990, there were nearly 20 pharmaceutical companies with large antibiotic R&D programs. Today, alarmingly, only a few companies remain. Not only does the tumbling private investment in antibiotics R&D jeopardize the development and availability of sorely needed new antibiotics in the United States, it also drains indispensable jobs and intellectual capital as companies seek to do business in other countries. For example, the regulatory environment for antibiotics in the European Union (EU) is viewed much more favorably by pharmaceutical companies and antibiotic public/private collaborations are being pursued as part of the EU's Innovative Medicines Initiative.[1]

Antibiotics' R&D poses unique scientific, regulatory and economic challenges. One company reports that over a 10 year period, it took 72 lead candidate antibiotic compounds in the early discovery phase to yield one FDA-approved product; other drug categories only took 15 leads to yield an FDA approval. Antibiotics also provide less financial reward for companies as they are used for a short duration, typically are priced low, and must be held in reserve to protect against the development of drug resistance, rather than used widely as most other drugs are.

We are encouraged that Congress has shown a strong interest in addressing the antibiotic crisis, as evidenced by the development of a U.S. Senate working group, past hearings in the U.S. House of Representatives, and pending antibiotic R&D incentives legislation. We call upon Congress to follow through with action that will spur new antibiotic R&D. A combination of push and pull incentives is needed to sufficiently raise the net present value of antibiotics so that they may compete on a level playing field with other drug categories for companies' R&D resources.

It is also vitally important for Congress to incentivize the development of new related diagnostics, and we are pleased that pending antibiotic R&D incentives legislation begins to address this issue. Better diagnostics can reduce the costs of new antibiotic development by identifying patients who are eligible for clinical trials. Diagnostic tests also are important for conducting surveillance for the patterns of antimicrobial resistance and recognizing emerging drug resistance. In addition, rapid diagnostic tests improve physicians' ability to prescribe antimicrobial drugs appropriately, which is critical to limit the development of resistant bacteria and preserve these important drugs' effectiveness for as long as possible. Congress should strengthen federal efforts to promote the appropriate use of antibiotics in health care facilities.

We are gravely concerned about the increasing number of patients with serious, life-threatening infections who cannot be treated due to a lack of effective antibiotics. These cases result in longer hospital stays, readmissions, increased healthcare costs and even deaths. Losing antibiotics entirely—which is where we are heading without urgent action—will undermine the way medicine is practiced and have devastating consequences for patients. We have an obligation to our children and grandchildren to invest in the development of new antibiotics and related diagnostic tests and to preserve antibiotics' effectiveness for the long term.

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[1](http://www.imi.europa.eu/sites/default/files/uploads/documents/Future_Topics/IMI_AntimicrobialResistance_Draft20120116.pdf).

Sincerely,

Alliance for Aging Research
Alliance for the Prudent Use of Antibiotics
American Academy of Allergy, Asthma and Immunology
American Academy of Neurology
American Academy of Ophthalmology
American Academy of Orthopaedic Surgeons
American Academy of Otolaryngology-Head and Neck Surgery
American Academy of Pediatrics
American Association of Hip and Knee Surgeons
American Association of Neurological Surgeons
American College of Emergency Physicians
American College of Medical Quality
American College of Rheumatology
American College of Surgeons
American Congress of Obstetricians and Gynecologists
American Geriatrics Society
American Physical Therapy Association
American Public Health Association
American Society for Microbiology
American Society of Hematology
American Thoracic Society
American Urological Association
Association for Professionals in Infection Control and Epidemiology
Center for Hospital Innovation and Improvement
Children's Hospital Association
Coalition of State Rheumatology Organizations
Congress of Neurological Surgeons
Department for Professional Employees of AFL-CIO
First Focus
Food Animal Concerns Trust
Heart Rhythm Society
HIV Medicine Association
Immune Deficiency Foundation
Infectious Diseases Society of America
National Alliance to Advance Adolescent Health
National Association of County and City Health Officials
National Association of Nurse Practitioners in Women's Health
National Association of Pediatric Nurse Practitioners
National Association of Veterans' Research and Education Foundations
National Coalition of STD Directors
National Family Planning & Reproductive Health Association
National Foundation for Infectious Diseases
Pediatric Infectious Diseases Society
Premier

Renal Physicians Association
Society for Healthcare Epidemiology of America
Society of Infectious Diseases Pharmacists
Society of Critical Care Medicine
Treatment Action Group
Trust for America's Health

[A similar letter has been sent to U.S. Senate leaders]

Mr. PITTS. I thank the gentleman and recognize the gentleman from Georgia, Dr. Gingrey, for 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you. I am going to start out with Dr. Eisenstein. I almost said Dr. Einstein after reading his résumé, and I am most impressed with that.

Dr. Powers testified that almost half of antibiotics approved since 1980 have disappeared from the market, either because of safety and efficacy issues or because of poor sales because the drug did not address public health needs. This is a question. Do you agree with Dr. Powers that current FDA oversight of antibiotics and the reality that market forces such as poor sales will help ensure generally that only those drugs that provide an unmet need will ultimately find their way to the market, or most importantly, be financial wins for the drug companies? Is that enough?

Mr. EISENSTEIN. Well, I agree that for a drug to be successful needs to demonstrate utility with patients. What the FDA process does is provide evidence of efficacy and safety. It doesn't translate necessarily to effectiveness, which is what happens in the broad population. That said, with the enormity of medical need that we presently have with the enumerated organisms plus others that I can talk about if you like, there is clearly a medical need and there is clearly a market failure in terms of being able to provide the appropriate incentives for companies to be able to make the investments in antimicrobials, and it appears that all of my colleagues on this committee are in complete agreement with that notion. That is again why I feel the GAIN Act as presently designated does provide exactly that sort of assistance.

Mr. GINGREY. Well, I thank you for that, and there was one part of Dr. Powers' testimony, and maybe he will have time, Mr. Chairman, to respond to this as well, but I want to stay with Dr. Eisenstein for just a second. In regard to your comments in your testimony about the GAIN Act, the fact that we have been working on it for a number of years, it has wide bipartisan support, especially here on the Health Subcommittee of Energy and Commerce and listing these pathogens, these known pathogens, and I reference that in my opening remarks, whether it is MRSA or whether it is some Gram-negative—we talked about the Iraqibacter problem with the troops returning from Operation Iraqi Freedom and other conflicts. It is important, I think, and I think you pointed it out, that these are known pathogens.

Now, Dr. Powers is suggesting that nobody comes in and says oh, this Klebsiella is killing me or I can't stand this Iraqibacter—you know, they say well, I am coughing and I think I may have pneumonia or I have got this horrible skin infection and my skin is sloughing off—to make a case for I guess some change to this carefully worked on piece of legislation, the GAIN Act, and to me, if I could make an analogy in the criminal justice system to say that if you have got a known thief out there that you don't make every effort to apprehend him or her, but rather you take all your law enforcement and your security measure and you pick two or three banks in the local neighborhood to protect because those are the areas where he might strike next. I don't know if that is a great analogy but I hope everybody understands the point I am trying to

make. What say you about that? And then I will go to Dr. Powers and let him comment on that.

Mr. EISENSTEIN. It is absolutely true what Dr. Powers says, that bugs by themselves don't mean that one has disease. If I were to look around the room here, that may be, what, 50 or 80 folks in the room, probably 20 of us have staph aureus and maybe 30 of us have staph aureus in our noses right now, and that about a third of the people that walk in this room have staph in their noses all the time, and the two-thirds left, about half of those have staph that come and go at various times, and we are seeing increasing numbers of those staph being MRSA staph. So perhaps 10 of us are walking around with MRSA staph in our noses right now, and yet, as an infectious disease physician, I wouldn't think about treating any of us for any of that. One has to have a condition, a disease, that says I am an infection causing a problem for this patient that goes along with certain manifestations. If it is pneumonia, the patient will have cough, will have shortness of breath, will have chest pain, will have fever. There are a constellation of methods that one can detect that. You are a physician as well. You understand that one makes the diagnosis based on what the patient shows, what the patient is saying, what your own examination of the patient shows.

That said, if the patient appears to have a pneumonia and you are able to recover a pure culture of staph aureus from the expectorated sputum, you know that the patient is suffering from staphylococcal pneumonia, and every hour that goes by that you don't treat that patient, the likelihood of the patient dying goes up significantly, and if we don't get drugs on board fast enough, we may lose 25 to 30 percent of even relatively healthy individuals.

Mr. GINGREY. To put it in really simple terms, and I know I am beyond my time, Mr. Chairman, I appreciate it, I will yield back, but it is like closing the barn door after the horse is long gone, so I thank you very much for that response.

Dr. Powers, I apologize. I didn't have time to go you.

Mr. PITTS. Dr. Powers, if you would like to respond?

Mr. POWERS. Sure, I would. I mean, I understand what you are saying. To use your thief analogy would be sort of like saying—and first I want to say, I think everyone is very appreciative about GAIN because we absolutely need to do something about this, and I think the question that I tried to bring up in my testimony is, can we focus the bill so we make sure that we do what we think we want to do without causing more harm. So I guess the concern is that, you know, if you see a bank robber and he is wearing a blue coat and the police say we are going to go out and arrest everybody who is wearing a blue coat, and so the thing that Dr. Eisenstein brought up is, these same organisms can cause less-serious disease and they can also cause more-serious disease.

And Dr. Gingrey, all the diseases listed when you spoke earlier to Dr. Woodcock, they are all serious ones, but FDA actually has approved 64 new drug applications for these same kinds of organisms for non-serious, non-life-threatening diseases since 1980. So that is why I think the history shows, and also those are the more profitable areas to go because those less-severe infections are more common in patients. So I think that is the issue of trying to focus

it to—we are all talking about serious and life-threatening diseases here. The question is if that is what we are talking about, could we actually focus the bill to that.

Mr. PITTS. The Chair thanks the gentleman and recognizes the ranking member of the full committee, Mr. Waxman for 5 minutes for questions.

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

Dr. Powers, let me pursue that issue with you. The GAIN Act seeks to create incentives that would prompt drug companies to develop and market new antibiotics. Specifically, it would give 5 years additional exclusivity if a company gets a new antibiotic approved. If we are talking about giving such a generous reward to companies, I think we need to ensure that two things are in place at a minimum. First, we need to make sure that we are only providing exclusivity for the kinds of drugs that will truly benefit the public health. Only antibiotics to treat dangerous infections for which we do not already have effective treatment should be covered in my opinion.

As currently written, the bill would provide exclusivity for drugs if they are targeted to treat specified bacteria. Some including you have expressed concern that this kind of model is both inappropriate and unusual for the FDA, and have instead suggested that we look at targeting drugs that treat specific infections instead of just bacterial species. More significantly, some believe that GAIN should be limited to new antibiotics for treating serious infections for which there is an unmet medical need. Can you explain a bit more about why focusing on specific infections is appropriate and why we should reserve incentives for drugs that treat serious infections with unmet medical need?

Mr. POWERS. Again, I think the issue is that antibiotics can be used to treat a wide array of infections caused by the same exact organism, and I can give an example of when I worked at FDA, several companies came in asking for indications for pneumonia that was caused by multi-drug-resistant organisms. Now, that was completely appropriate. At the same time, they asked for approval for multi-drug-resistant organisms for sinus infections and ear infections in kids and other things that predominantly get better on their own, sometimes even without antibiotics. So the history of what has happened before shows that—and in a sense, you can't blame a company for asking. FDA didn't grant those, though, because they applied the same exact standard that we are talking about today. It is not clear whether resistance in the test tube has much of an impact on patient outcomes in a disease where people will get better anyway. So it seems to make sense to focus on the areas of where, when you have a resistant disease, that is what is going to kill you.

The other thing is that this sort of comports with everything that FDA has ever done in the past related to providing incentives. Priority Review, Accelerated Approval that we are talking about today, and Fast Track designation as well as subpart E approvals all are based on serious and life-threatening diseases, unmet medical needs and added benefit above available therapies. So it fits in with the regulatory paradigm already, which of course would make it easier to implement as well.

Mr. WAXMAN. Well, the second thing I think needs to be in place is a robust stewardship program. We need to make sure that any antibiotics that are approved under this kind of new system are protected once they are on the market. We have seen far too many antibiotics lose their effectiveness because the bugs they seek to treat become resistant, and that is a problem caused in large part by overuse of these drugs. So we need to make sure that doesn't happen with these new antibiotics that we have all invested so much in, after all. When extended exclusivity is granted, we all pay higher drugs for a longer period of time. Do you agree with that concept?

Mr. POWERS. I think that is absolutely key, and they have to go hand in hand. To pass something about giving incentives to develop new drugs now hoping that we will approve something about stewardship later probably doesn't make a whole lot of sense. These really need to be linked to each other because developing new drugs without the ability to use them in the appropriate places they need to be used is really a dangerous thing. That is kind of how we got to where we are today.

Mr. WAXMAN. Can you elaborate more on what ideas you have about stewardship?

Mr. POWERS. I think that there is—I put a couple in my testimony in terms of how I think that allowing FDA to have the authority to designate where drugs should be used appropriately is a big step. In the past, FDA has had the authority to restrict drugs where they weren't safe and effective. Here we would be saying well, maybe these drugs could be used in less life-threatening diseases but we really think they ought to be reserved for these specific serious diseases. That would be novel. So I think giving FDA the authority to do that would be really important.

The other thing is, having been on the Interagency Task Force myself, I know somebody said to me once, you know, it is different when it is your 25th job at the bottom of your list of things to do versus you come into work and every day that is exactly what you have to focus on. So I think developing an HHS-level internal group that consists of agencies that address this problem might highlight the issues associated with antibiotic resistance and allow people to spend their time focusing on it.

Mr. WAXMAN. Thank you very much.

Mr. PITTS. The Chair thanks the gentleman and recognize the gentleman from New Jersey, Mr. Lance, for 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman.

Mr. Chairman, I ask unanimous consent to place in the record letters of support for the Medical Gas Safety Act from the Compressed Gas Association and three manufacturers: Air Products, AirGas and Tri-Gas.

Mr. PITTS. Without objection, so ordered.

[The information follows:]

COMPRESSED GAS ASSOCIATION
14501 George Carter Way, Suite 103, Chantilly, VA 20151
(703) 788-2700 ■ Fax: (703) 961-1831 ■ E-mail: cga@cganet.com ■ Web Site: www.cganet.com

December 12, 2011

Honorable Leonard Lance
United States House of Representatives
426 Cannon House Office Building
Washington, DC, 20515

Dear Representative Lance,

On behalf of the Compressed Gas Association (CGA), I am writing to thank you for your co-sponsorship of H.R. 2227, the Medical Gas Safety Act, and to request your assistance in enacting this legislation as a part of Congress' consideration of the Prescription Drug User Fee Act (PDUFA) reauthorization to address several significant issues regarding the regulation of medical gases by the Food and Drug Administration (FDA). CGA is an ANSI-approved safety standard setting organization for the medical gas industry. The current FDA regulatory regime for medical gases has created considerable uncertainty and driven up compliance costs for our industry as individual federal and state inspectors attempt to apply regulations designed for traditional pharmaceuticals to medical gases.

Medical gases are a unique class of drugs that have been used as drugs for over 100 years. Today, medical gases are used daily by over a million patients to treat a variety of medical conditions. Medical gases typically consist of elements, or mixtures of elements, including oxygen, nitrogen, nitrous oxide, carbon dioxide, helium and medical air.

The manufacturing and distribution process for medical gases is distinct from any other class of drugs. Unlike traditional pharmaceuticals, over 99% of the volume of medical gases are manufactured by separating air into pure elements and filling those elements, or mixture of elements, into high-pressure cylinders rather than compounding chemical components into pills or injectibles. Due to the unique characteristics of medical gases, our industry consists of over 3,400 manufacturing and distribution facilities located in every state that distribute product in a limited geographic area rather than a few large manufacturing sites that distribute product worldwide. In fact, approximately *half of all registered drug facilities are medical gas manufacturers*, 93% of which, according to FDA, are small businesses.

We have attempted to work collaboratively with FDA for over 35 years to address these recurring issues. We have submitted two outstanding Citizens Petitions (filed in1979 and 1994), submitted constructive public comments to pending regulations and draft guidance and held numerous meetings with FDA staff to educate them on the unique characteristics of medical gases and the many regulatory issues that result from FDA's current regulatory regime. Despite this time consuming process, and because FDA never codified the regulatory differences, our industry remains under an uncertain regulatory regime enforced through a confusing system of

FDA enforcement discretion and reliance on draft guidance labeled as "for comment purposes only" and "Not for Implementation" that was never finalized to incorporate the large number of comments filed to the docket.

Therefore, at this juncture there is a need for legislation to provide certainty and consistency for our industry by creating a pathway for medical gas approval and targeted cGMP regulations to resolve these decades old regulatory issues. H.R. 2227 will create a path forward that will provide certainty for regulators and the medical gas industry. We expect similar legislation will be introduced in the Senate soon. We believe that the legislative provisions included in this legislation are necessary to ensure that our patients continue to have access to safe medical gases.

As the safety standard setting organization representing thousands of jobs in the medical gas industry, I respectfully request your support in enacting the reforms contained in H.R. 2227, to reform the FDA system of regulation of medical gases, as a part of the PDUFA reauthorization process in 2012. This legislation will be critical to solving regulatory and approval issues that have been unaddressed due to the low risk profile of our industry or poorly addressed due to a lack of understanding how the medical gas industry differs from the traditional drug industry.

Thank you for being a co-sponsor of H.R. 2227 and for your assistance to help include this legislation as a part of the reauthorization of PDUFA. I look forward to working with you and your staff to enact H.R. 2227 and to solve these long-standing regulatory issues.

Sincerely,

Michael Tiller
President
Compressed Gas Association

Air Products and Chemicals, Inc.
7201 Hamilton Boulevard
Allentown, PA 18195-1501
Telephone (610) 481-4911

January 9, 2012

VIA E-MAIL or FACSIMILE 202-225-5361

Honorable Leonard Lance
United States House of Representatives
426 Cannon House Office Building
Washington, DC 20515

Dear Representative Lance,

I am writing to thank you for sponsoring H.R. 2227, the "Medical Gas Safety Act," which will address several pressing issues regarding the current regulation of medical gases by Food and Drug Administration (FDA). I respectfully request your assistance to work with the Energy & Commerce Committee to enact this legislation as a part of Congress' consideration of the Prescription Drug User Fee Act (PDUFA) reauthorization. The current regulatory system creates significant uncertainty for our employees in your state and across the country when individual federal and state inspectors attempt to apply a regulatory scheme designed for traditional pharmaceuticals to medical gases.

Our company manufactures medical gases, like Oxygen, for patients under a physician's prescription. Medical gases have been used as drugs for over 100 years and are used daily by over a million patients to treat a variety of medical conditions. Most medical gases pre-date the new drug application (NDA) process and, consequently, have always been sold without an NDA. Unlike traditional pharmaceuticals, medical gases are typically manufactured by heating and cooling air to separate it into pure elements and filling those elements, or mixture of elements, into high-pressure cylinders.

In 1976, FDA committed to create separate regulations for medical gases that would incorporate the unique characteristics of medical gases. However, no such regulations have been established, requiring a complex system of enforcement discretion to apply a regulatory scheme designed for traditional pharmaceuticals to our products. Recently, our industry has been facing increasing regulatory issues due to the FDA's new "Unapproved Drug Initiative" and confusion over how to apply regulations like expiration dating to medical gases like Oxygen that never expire. These issues create significant uncertainty and drive up compliance costs for our industry.

H.R. 2227 will reform the FDA system of regulation of medical gases and provide certainty to patients, medical gas manufacturers and federal and state regulators. This legislation is critical to solving decades old regulatory and approval issues that have been left unaddressed due to the low risk profile of our industry. We are working in coordination with the Compressed Gas Association, the safety standard setting organization for our industry, on this legislation.

On behalf of our employees in New Jersey, I thank you for sponsoring H.R. 2227 and ask for your support to enact this legislation as a part of the reauthorization of PDUFA.

Sincerely,

Joseph M. Pietrantonio
Vice President, Global Operations
Air Products and Chemicals, Inc.

Airgas

Airgas, Inc.
259 North Radnor-Chester Road
Suite 100
Radnor, PA 19087-5283
Tel : 610- 902-6037
http://www.airgas.com
tom.thoman@airgas.com

December 29, 2011

Honorable Leonard Lance
United States House of Representatives
426 Cannon House Office Building
Washington, DC 20515

Dear Representative Lance,

I am writing to thank you for sponsoring H.R. 2227, the "Medical Gas Safety Act," which will address several pressing issues regarding the current regulation of medical gases by Food and Drug Administration (FDA). I respectfully request your assistance to work with the Energy & Commerce Committee to enact this legislation as a part of Congress' consideration of the Prescription Drug User Fee Act (PDUFA) reauthorization. The current regulatory system creates significant uncertainty for our employees in your state and across the country when individual federal and state inspectors attempt to apply a regulatory scheme designed for traditional pharmaceuticals to medial gases.

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In 1976, FDA committed to create separate regulations for medical gases that would incorporate the unique characteristics of medical gases. However, no such regulations have been established, requiring a complex system of enforcement discretion to apply a regulatory scheme designed for traditional pharmaceuticals to our products. Recently, our industry has been facing increasing regulatory issues due to the FDA's new "Unapproved Drug Initiative" and confusion over how to apply regulations like expiration dating to medical gases like Oxygen that never expire. These issues create significant uncertainty and drive up compliance costs for our industry.

H.R. 2227 will reform the FDA system of regulation of medical gases and provide certainty to patients, medical gas manufacturers and federal and state regulators. This legislation is critical to solving decades old regulatory and approval issues that have been left unaddressed due to the low risk profile of our industry. We are working in coordination with the Compressed Gas Association, the safety standard setting organization for our industry, on this legislation.

On behalf of our more than 250 employees in New Jersey, I thank you for sponsoring H.R. 2227 and ask for your support to enact this legislation as a part of the reauthorization of PDUFA.

Sincerely,

Thomas S. Thoman
Division President - Gas Production
Airgas, Inc.

December 28, 2011

VIA FACSIMILE 202-225-5361

Honorable Leonard Lance
United States House of Representatives
426 Cannon House Office Building
Washington, DC 20515

Dear Representative Lance,

I am writing to thank you for sponsoring H.R. 2227, the "Medical Gas Safety Act," which will address several pressing issues regarding the current regulation of medical gases by Food and Drug Administration (FDA). I respectfully request your assistance to work with the Energy & Commerce Committee to enact this legislation as a part of Congress' consideration of the Prescription Drug User Fee Act (PDUFA) reauthorization. The current regulatory system creates significant uncertainty for our employees in your state and across the country when individual federal and state inspectors attempt to apply a regulatory scheme designed for traditional pharmaceuticals to medial gases.

Our company manufactures medical gases, like Oxygen, for patients under a physicians prescription. Medical gases have been used as drugs for over 100 years and are used daily by over a million patients to treat a variety of medical conditions. Most medical gases pre-date the new drug application (NDA) process and, consequently, have always been sold without an NDA. Unlike traditional pharmaceuticals, medical gases are typically manufactured by heating and cooling air to separate it into pure elements and filling those elements, or mixture of elements, into high-pressure cylinders.

In 1976, FDA committed to create separate regulations for medical gases that would incorporate the unique characteristics of medical gases. However, no such regulations have been established, requiring a complex system of enforcement discretion to apply a regulatory scheme designed for traditional pharmaceuticals to our products. Recently, our industry has been facing increasing regulatory issues due to the FDA's new "Unapproved Drug Initiative" and confusion over how to apply regulations like expiration dating to medical gases like Oxygen that never expire. These issues create significant uncertainty and drive up compliance costs for our industry.

H.R. 2227 will reform the FDA system of regulation of medical gases and provide certainty to patients, medical gas manufacturers and federal and state regulators. This legislation is critical to solving decades old regulatory and approval issues that have been left unaddressed due to the low risk profile of our industry. We are working in coordination with the Compressed Gas Association, the safety standard setting organization for our industry, on this legislation.

On behalf of our 191 employees in New Jersey, I thank you for sponsoring H.R. 2227 and ask for your support to enact this legislation as a part of the reauthorization of PDUFA.

Sincerely,

Ted Schwarzbach
Executive Vise-President Risk Management
Matheson Tri-Gas, Inc.

Mr. LANCE. Thank you, Mr. Chairman.

To Mr. Walsh, can you give the committee a couple examples of why FDA's current regulations are not a good fit for medical gases?

Mr. WALSH. Sure. I think first of all, I would like to—because I don't think I testified for it, we do feel very fortunate that we have the FDA.

Mr. LANCE. Absolutely, and we are working well with the FDA and it is an excellent agency.

Mr. WALSH. We have existed before the FDA came along and then the two of us have been working down this precarious path of discretionary enforcement and we are fortunate that we share the same principles that we want to send our employees home safe at night and we want our patients to be safe, so I think that is critical to say to say that we have been keeping it together because we are fortunate that the CGA and the FDA work so closely together.

Having said that, the medical gases fall under a pharmaceutical standard yet our manufacturing processes are different, our containers that hold the drugs are different, and the characteristics of our drugs are different. From a manufacturing standpoint, a typical pharmaceutical company may have one plant that distributes their product nationally or perhaps even globally. We have 4,500 plants in the United States producing and selling oxygen, which occurs in a very tight radius of about 100 miles. And in terms of our containers, many of you probably have loved ones that you have seen on oxygen. They pull around a cylinder, which is about 2,000 psig under pressure. After it is empty, we pick it up, bring it back to our location and refill it. If the label, if you can still see the label and it is still in good working condition, it stays on there, or in large cases, you might see it at a hospital, a large cryogenic container where as it gets low, we come to fill it. You compare that to a typical disposal pill box that gets thrown away. And then the characteristics, most of our medical gases are on the periodic table. They never expire, which is very different from pharmaceuticals.

Mr. LANCE. Thank you, and what would the effect, in your opinion, be on patients if the FDA were to require an NDA, a New Drug Application, for medical gases?

Mr. WALSH. I think Dr. Woodcock said it very well today in her goals. It is having a safe, effective and available product, and what gets me particularly concerned is the available if we have to go through an NDA process. An NDA is a long process to go through. We have 2 million patients alone on oxygen in the homes, not to mention in hospitals and doctor offices. So it could really have an impact on supply to these existing patients that we are supplying. And to what safety benefit? Our products have been used—oxygen we used as an example has been used for over 100 years. You could Google it and find physicians talking about oxygen therapy in the 1850s.

Mr. LANCE. Thank you. Google it now, not 100 years ago.

Mr. WALSH. Google it now. Do not Google 100 years.

Mr. LANCE. Do you see some problems in particular of the current system for small business medical gas manufacturers?

Mr. WALSH. I do, and I said before, I started from a small business, and if would have known—I was very young when I started

the business, but if I would have known then what I know now, I would not have started that business because you are investing in something that is not approved. It is not under the approved drug status. Plus, if the FDA chose to enforce us to a strict pharmaceutical standard, many of the small companies would get out of the medical gas business.

Mr. LANCE. Thank you. I look forward to working with Dr. Woodcock on this issue and with those on the panel, and with that, Mr. Chairman, I yield back the balance of my time.

Mr. PITTS. Do you have a follow-up?

Mr. GINGREY. Mr. Chairman, I do, and thank you for yielding. First I would like to ask unanimous consent to submit a letter, a statement from the California HealthCare Institute in support of H.R. 2182, the GAIN Act. Do I have unanimous consent to submit that for the record, Mr. Chairman? Mr. Chairman, I thank you for that, and I know the ranking member would like to look at it, and that is appropriate. I did want to ask one follow-up question if you will allow.

This issue of stewardship, and again, I will go back to Dr. Eisenstein. This issue of stewardship, the judicious use of antibiotics, and this has come up a few times in testimony, and for members of the panel today and from the committee members, in fact, the ranking member of the committee. So I want to ask you this: Dr. Eisenstein, can we solve global resistance through a Congressionally mandated stewardship program? And I think Dr. Powers referred to this as well. Are other forms like maybe the World Health Organization better suited to tackle this issue of antibiotic resistance from overuse, over-prescribing, etc.?

Mr. EISENSTEIN. That is an excellent point. The problem with drug-resistant organisms, Dr. Gingrey, as you know, is they know no boundary. So when the New Delhi beta beta-metallo proteinase was discovered in strains of Klebsiella and other Gram-negatives in India, within 6 to 12 months we saw patients infected in the United States, in Canada, in the United Kingdom, etc. I was at a meeting recently where an individual went to an unnamed southeastern country in Asia and showed five different pharmacies, one after another, where any individual could go into any one of those stores and choose any antibiotic essentially that they wanted. This is a much broader problem, and clearly, stewardship must be part of the solution. I would submit, though, that that is not the place for the GAIN Act.

Mr. GINGREY. Well, I thank you for that, and very quickly, Mr. Chairman, I will go to Dr. Powers now.

Dr. Powers, you had sort of suggested just a few minutes ago that maybe there ought to be some Federal mandate in regard to best practices and how infectious disease specialists such as yourself should prescribe antibiotics in the most judicious and efficacious manner. It would seem to me that maybe that should come from the American Academy of Infectious Disease Subspecialists and their best practices paradigm, but you seem to think, if I understand your testimony correctly, that maybe the Federal Government should do that. Would you suggest that that would be within the auspices of the FDA or maybe from some other government bureaucracy such as IPAB?

Mr. POWERS. I don't think they are mutually exclusive. To answer the question you asked to Dr. Eisenstein, resistance is both global and local, and that is that there have been countries where their antibiotic usage has decreased, where they have been able to decrease local resistance. That doesn't mean that we shouldn't have a global approach. I think what I was trying to suggest was that FDA should have the authority to be able to designate drugs for special uses. That doesn't mean they are regulating the practice of medicine or telling doctors how to use it, but having worked at FDA, I certainly understand the importance of giving doctors the information they need to be able to practice appropriately. That is more of what I was suggesting, not that FDA should designate who can use what. And I think that means working with those other outside organizations and developing stewardship programs at hospitals.

Mr. GINGREY. Thank you, Dr. Powers.

And Dr. Eisenstein wanted to make another comment. Is that OK, Mr. Chairman?

Mr. PITTS. Yes.

Mr. EISENSTEIN. Yes, just to continue on two points that I would like to make, or actually three points. One of them, in terms of the FDA being able to approve a drug because it happens to get a very bad organism, you still have to—the manufacturer still has to go through normal procedures to demonstrate efficacy, which means that the drug is better than placebo and that the agency has got to designate it, therefore approved on that basis. That is point number one.

Point number two, the practice of medicine, as you know as a former practicing physician, has changed dramatically over 40 years. I graduated from medical school 40 years ago, and antibiotics were used essentially willy-nilly at that time. In the last 10, 15 years, the stewardship that we see already in place in hospitals is so exact, we could not get our own antibiotic on formularies anywhere in this country without it being severely restricted so that only infectious disease experts were able to give the approval for the use of that drug, and in part, because of that, we believe Cubicin, the drug that we now have had approved for 8 ½ years, still has a 99.9 percent susceptibility rate against MRSA despite 8 ½ years on the market. So we can use drugs appropriately and they have been used appropriately.

And lastly, I would just like to wholeheartedly agree with the Society of Infectious Disease Pharmacists who noted that inclusion of stewardship language in the GAIN Act may broaden the scope of the act and take the focus away from the appropriate incentives that we are talking about. If you try to put too much in the way of disincentives back in this bill, you are actually creating the same problem that we are trying to solve.

Mr. PITTS. The Chair thanks the gentleman.

The unanimous consent request of Dr. Gingrey with the letters is approved.

[The information follows:]

C·H·I
CALIFORNIA HEALTHCARE INSTITUTE

Statement from the California Healthcare Institute on Legislative Action to Combat Antibiotic Resistance in the U.S.

Contact:
Nicole Beckstrand
beckstrand@chi.org
858-456-8881

(LA JOLLA, Calif., March 8, 2012) – California Healthcare Institute (CHI) President and CEO David L. Gollaher, Ph.D., issued the following statement regarding today's House Energy and Commerce Committee Subcommittee on Health hearing, "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain," where issues related to antibiotic development – including the Generating Antibiotic Incentives Now (GAIN) Act – were discussed:

"Since their discovery, antibiotics have improved the quality and length of life for countless people globally. The widespread use of antibiotics has accelerated the emergence of microbial resistance, weakening their effectiveness in treating evolving pathogens. In the U.S. alone antibiotic resistance infections cause 100,000 deaths each year.

While the threat of antibiotic resistance is becoming more prevalent, the drug development pipeline has substantially slowed down. Antibiotic approvals by FDA from 1983 to 2007 declined by 75 percent. The threat of antibiotic resistance faces economic, scientific and regulatory barriers.

To address this growing public health crisis, the Generating Antibiotic Incentives Now (GAIN) Act, a bipartisan and bicameral effort led by Reps. Phil Gingrey (R-GA), M.D. and Anna Eshoo (D-CA) in the House and Sens. Richard Blumenthal (D-CT) and Bob Corker (R-TN) in the Senate, was introduced in 2011 to help spur the development of new antibiotics. The GAIN Act provides the necessary economic incentives for innovator companies to encourage investment in antibiotics and supports expedited approval.

Given the importance of developing new antibiotics, CHI urges Congress to support the GAIN Act, and encourages FDA to reconsider its regulatory pathway. This legislation will help rebuild our nation's antibiotic pipeline and is a critical first step toward addressing antibiotic resistance.

CHI supports further improving the FDA processes and management to better reflect the rising and urgent medical and public health needs resulting from regulatory uncertainty and unpredictability in the antibiotics space. Including the GAIN Act into must-pass legislation – the Prescription Drug User Fee Act (PDUFA) – is the best and only opportunity for Congress to address the issue of antibiotic resistance in

2012. We believe that industry, government and regulators must work together to develop ways to encourage adequate investment in antibiotic development."

To read more about CHI's initiative to promote antibiotic discovery and development, or about the GAIN Act, click here.

About CHI
CHI represents more than 275 leading biotechnology, medical device, diagnostics, and pharmaceutical companies, and public and private academic biomedical research organizations. CHI's mission is to advance responsible public policies that foster medical innovation and promote scientific discovery. CHI's website is www.chi.org. Follow us on Twitter @calhealthcare, Facebook, LinkedIn and Youtube.

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Mr. PITTS. The Chair recognizes the ranking member for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman. I just wanted to ask Mr. Walsh, you heard Dr. Woodcock, who is still here, on the first panel say that FDA is concerned with the concept of creating an entirely new regulatory structure for medical gases, and she said she would be willing to meet with you personally to discuss whether there are other ways to addressed the Compressed Gas Association's concern short of legislation. So I am trying to get you together here, you see? Would you be willing to meet with Dr. Woodcock to see if there is a different solution here?

Mr. WALSH. We definitely have an interest in working directly with Dr. Woodcock and her staff to come up with the actual legislation that can give us the guidelines and regulations specific for medical gases.

Mr. PALLONE. OK. Because I think it sounds like you have some valid concerns but I just hope the FDA can be responsive and find a way to resolve these issues without actually having to pass legislation. That is my hope, so we will see if you can get together. It would be helpful.

Mr. WALSH. I do think legislation is important. We have been operating under the guidelines for many, many years, and so I think it is important that we have something very strict and by law that we can operate off of.

Mr. PALLONE. All right. Well, let us see what develops out of the meeting in any case. Thank you.

Mr. PITTS. The Chair thanks the gentleman, and I would like unanimous consent to enter into the record statements from the National Association of Chain Drugstores, and Pharmaceutical Research and Manufacturers of America. I think you have seen this. Without objection, so ordered.

[The information follows:]

Statement

Of

The National Association of Chain Drug Stores

For

U.S. House of Representatives
Energy and Commerce Committee
Subcommittee on Health

Hearing on:

FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain

March 8, 2012
10:15 a.m.
2322 Rayburn House Office Building

National Association of Chain Drug Stores (NACDS)
413 North Lee Street
Alexandria, VA 22314
703-549-3001
www.nacds.org

The National Association of Chain Drug Stores (NACDS) thanks the Members of the Subcommittee on Health for consideration of our statement for the hearing on "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain."

We believe that the U.S. supply chain is safe, if not the safest in the world. NACDS and the chain pharmacy industry are committed to partnering with policymakers and the supply chain stakeholders on viable effective strategies to enhance the safety and security of the U.S. prescription drug distribution supply chain. Our members have invested significant resources and efforts towards this goal, including changes in purchasing practices and actively supporting state legislation that strengthened the supply chain integrity. Nothing is more important to our industry than the health and safety of our patients.

As lawmakers, we urge you to consider approaches that are feasible and workable for the supply chain, and to recognize the importance of not requiring untested costly mandates such as a prescription drug "track and trace" system for supply chain stakeholders. Such requirements would add billions in additional costs to the healthcare system and take time and resources away from pharmacies' ability to provide pharmacy services to their patients.

NACDS represents traditional drug stores, supermarkets, and mass merchants with pharmacies – from regional chains with four stores to national companies. Chains operate more than 40,000 pharmacies and employ more than 3.5 million employees, including 130,000 pharmacists. They fill over 2.6 billion prescriptions annually, which is more than 72 percent of annual prescriptions in the United States. The total economic impact of all retail stores with pharmacies transcends their $900 billion in annual sales. Every $1 spent in these stores creates a ripple effect of $1.81 in other industries, for a total economic impact of $1.76 trillion, equal to 12 percent of GDP. For more information about NACDS, visit www.NACDS.org.

This statement will discuss the following matters on behalf of NACDS and our members:

- The Food and Drug Administration's PDUFA goals

- Enhancing Supply Chain Security and the Pharmaceutical Distribution Security Alliance
- Registry of Safe Online Pharmacies - Targeting Illegitimate Internet Drug Sellers
- The Role of Pharmacy Medication Therapy Management (MTM)
- Improved Patient Medication Information "One Document" Solution

NACDS and the chain pharmacy industry look forward to working with Members of Congress on issues related to enhancing the security and integrity of the U.S. prescription drug supply chain.

THE FOOD AND DRUG ADMINISTRATION'S PDUFA GOALS

We are pleased that FDA has proposed to apply user fees toward efforts to enhance and modernize the U.S. drug safety system. To enhance patient safety, FDA plans to devote user fees toward reviewing drug applications for look-alike and sound-alike proprietary names and related factors that could contribute toward medication errors such as unclear label abbreviations, acronyms, dose designations, and error-prone label and packaging design. We wholeheartedly support this proposal that would reduce the potential for medication errors throughout the healthcare delivery system.

We are also supportive of FDA's plans to utilize user fees to develop techniques to standardize prescription drug Risk Evaluation and Mitigation Strategies (REMS) and better integrate them into the existing and evolving healthcare system. The success of any REMS is highly dependent on the ability of all relevant stakeholders to provide ample input during the design phase of the program, well before implementation. The concerns of pharmacies and other healthcare providers must be considered in order for REMS to be successful. Since REMS could impact pharmacy operations and workflow and even a pharmacy's ability to provide the affected medication to a patient, we welcome more opportunities to work with FDA to standardize REMS.

In addition, we strongly encourage FDA's proposal to develop methodologies for assessing whether REMS are achieving their goals of mitigating risks and assessing the effectiveness and impacts of REMS on patient access and on the healthcare system. We believe that REMS should be subject to review by pharmacies and other relevant healthcare providers, such as by a representative panel of expert reviewers to include pharmacists who practice in pharmacy settings affected by the REMS. Although pharmacies are not directly responsible to FDA for the design, implementation, and success of REMS, pharmacies are subject to the elements of REMS in order to meet the needs of their patients.

ENHANCING SUPPLY CHAIN SECURITY AND INTEGRITY

While steps can be taken to further strengthen the U.S. drug distribution system, it is important to remember that the domestic drug supply chain is one of the safest in the world. NACDS and the chain pharmacy industry stand ready to work with federal lawmakers and other stakeholders on workable strategies to advance supply chain security.

In addition, our industry has been engaged at the state level to enhance supply chain integrity. We have supported enactment of state-level legislation requiring enhanced wholesale distributor licensure requirements and chain of custody "pedigrees" for drug distributions outside the recognized and safe "normal distribution channel." More than 60% of the states have enacted laws and regulations to strengthen the security of the drug distribution supply chain. We have also supported increased fines and penalties for violations of these state laws. Our members have seen marked improvements in the security of the drug distribution supply chain since the adoption of these initiatives and state laws.

We believe that the security of the U.S. prescription drug distribution supply chain requires the commitment of all supply chain stakeholders working together to maintain and implement feasible and achievable security measures. To that end, NACDS has participated in numerous supply chain coalitions over the past ten or more years to consider additional supply chain security measures.

Most recently, NACDS and some of our members participated with an informal coalition of drug manufacturers and wholesalers and their associations and the National Community Pharmacists Association (NCPA) to consider supply chain security measures. This group, originally known as the Consortium and now known as the *Pharmaceutical Distribution Security Alliance* (PDSA), has been working together for more than ten months. NACDS is pleased to be a member of PDSA, and wishes to highlight PDSA's hard work and efforts in developing a Discussion Draft that was recently provided to federal policymakers.

NACDS supports a number of the policies in the PDSA Discussion Draft. For instance, we support adoption of strong uniform federal requirements for wholesaler drug distributor licensure coupled with federal preemption of state laws. Notably, however, states will retain licensure authority. The requirements would operate as both a floor and a ceiling so that *all states have the same requirements,* thereby avoiding a patchwork of states laws. Most importantly, this would block unscrupulous entities from "gaming" the system by moving across state lines in search of less stringent laws.

We also support the federal preemption provision in the PDSA Discussion Draft that would preempt state pedigree and drug tracking and tracing requirements. For any enhancements to the supply chain security, a national approach with preemption of states is essential. Supply chain stakeholders operate in a number of states. A patchwork of state requirements is unworkable and will hinder the timely and efficient distribution of drugs across the nation.

We are also supportive of the prescription drug lot level tracing approach in the PDSA Discussion Draft. However, we have some concerns with the language as drafted. We are discussing with PDSA several conforming, clarifying and technical edits to the Discussion Draft that will address the important concerns of our members related to wholesale drug distribution and change of ownership, responsibility for determination of counterfeit drug products, tracing by lot number, providing human and machine readable information on drug products, drug returns, data security and technical

edits. It is our plan to reach agreement with PDSA on these matters, and conversations have already begun.

Chain pharmacy remains committed to working with Congress on the security of the U.S. drug distribution supply chain. However, we remain concerned with potential mandates to track and trace prescription drugs due to disruptions, complexities, and the substantial resources that would be required to comply with such mandates. We support pursuing policies that would make health care more efficient and affordable, not unnecessarily increase healthcare costs.

REGISTRY OF SAFE ONLINE PHARMACIES - TARGETING ILLEGITIMATE INTERNET DRUG SELLERS

NACDS also believes that addressing the problem of illegitimate Internet drug sellers is an important component of supply chain security. These illicit online drug sellers have websites that target U.S. consumers with ads to sell drugs often without any prescription required. They are almost without exception located outside of the U.S. yet have websites camouflaged to look like legitimate pharmacy websites. They operate in clear violation of U.S. state and federal laws and regulations that protect public health and safety. They sell drugs to consumers without the safety precautions of a legitimate prescriber-patient relationship, a valid prescription, and a licensed U.S. pharmacy.

These illegal Internet sites that profit from these illegitimate activities are often mistakenly referred to as Internet "pharmacies." They are not U.S. licensed pharmacies and do not comply with any of the rigorous state and federal laws governing pharmacy licensure and the practice of pharmacy by pharmacists.

We support legislation that has been introduced recently that will help stop these illicit online drug sellers. In December 2011, Senators Feinstein (D-CA) and Sessions (R-AL), introduced S. 2002, the Online Pharmacy Safety Act of 2011. In March 2012, H.R. 4095 was introduced by Representatives Cassidy (R-LA) and Ross (D-AR). These common sense bills will help prevent rogue online drug sellers from compromising the existing safeguards that protect Americans. The bill requires the U.S.

Department of Health and Human Services (HHS) to create a public registry of law-abiding pharmacy websites so that someone choosing to purchase medicine through an online pharmacy will have confidence in the source of their medication.

THE ROLE OF MEDICATION THERAPY MANAGEMENT (MTM)

Services provided by community pharmacists improve drug safety. Pharmacists are uniquely qualified to provide Medication Therapy Management (MTM) services to patients, which help ensure that patients are prescribed the correct medications and that they are taking them properly. Unfortunately however, MTM services are infrequently compensated, which limits pharmacists' ability to provide these services to patients.

When patients are prescribed the correct medications, they are less likely to experience adverse effects, such as allergies and drug interactions. Thus, they are more likely to take their medications as directed, that is, to adhere to their therapy. Properly reimbursing pharmacists for providing MTM services is a greatly underutilized tool for helping to ensure prescription drugs are used safely and effectively.

Pharmacist MTM services and the improved medication adherence that can result also provide the dual benefits of improving patient health outcomes and reducing the use of other more costly healthcare services. Research has shown that an estimated one-third to one-half of all patients in the United States do not take their medication as prescribed. They may fail to take their prescription medications, take their medication incorrectly, or stop taking their medication altogether. These circumstances seriously undermine quality of life and quality of care, patient outcomes and the value of healthcare dollars spent. Poor medication adherence costs the U.S. approximately $290 billion annually – 13% of total healthcare expenditures. Community pharmacies and their pharmacists are uniquely situated to assist patients in complying with their prescribed medication treatment and explaining the benefits of adherence. Programs such as ChecKmeds in North Carolina, a program where community pharmacists provided MTM services involving nearly 27,000 seniors in 2008 and 2009, showed the benefits and savings by avoiding more costly healthcare services such as

emergency rooms and hospitalizations and prescription drug savings. For every dollar spent in this program for pharmacist medication therapy management services, the benefit was $13.55 in savings.

IMPROVED PATIENT MEDICATION INFORMATION "ONE DOCUMENT SOLUTION"

As FDA has recognized, patients typically receive several different types of medication information, developed by different sources that may be duplicative, incomplete, or difficult to read and understand. We agree with FDA that the current patient medication information (PMI) is not adequate to ensure that patients receive essential information in a clear and easily understandable format. We are very pleased that FDA is holding public hearings to gather information to assist the agency with the adoption of a single PMI document that is standardized with respect to format and content, the "one-document solution." For each medication, patients want a single, useful document, designed and written for them, that recognizes their information needs, that focuses concisely on critical information, and that provides them with clear instructions on where to go for further advice and instruction.

Existing requirements for multiple medication information documents, containing redundant or even conflicting information, creates logistical and financial burdens for pharmacies that compromise effective patient counseling. It would be far more convenient, efficient, and ultimately more effective for pharmacists to counsel patients by providing a single PMI document that could easily be understood and facilitate a discussion concerning proper use of medication.

We support manufacturer development of PMI with FDA approval. Only this approach could absolutely ensure that all PMI meet FDA standards of accuracy and comprehensibility and properly balanced communication of risks and benefits. In our view, each FDA-approved drug would eventually have a single, standardized, manufacturer-developed, FDA-approved PMI document.

CONCLUSION

NACDS thanks the Subcommittee for consideration of our comments. We look forward to working with policy makers and stakeholders on these important issues.

Statement of the Pharmaceutical Research and Manufacturers of America (PhRMA)
Submitted for the Record to the House Energy & Commerce, Subcommittee on Health Hearing
"Downstream Pharmaceutical Supply Chain Issues"
March 8, 2012

PhRMA represents the country's leading pharmaceutical research and biotechnology companies. Our members are devoted to developing medicines that allow patients to live longer, healthier, and more productive lives, and are leading the way in the search for new cures and treatments. Our members alone invested an estimated $49.4 billion in 2010 in discovering and developing new medicines.

The U.S. ensures prescription drug safety in part by maintaining a closed system for the distribution of prescription medicines. In addition to the existing standards that require FDA approval of a New Drug Approval (NDA) application for new drugs, an Abbreviated New Drug Application (ANDA) for generic drugs, or a Biologics License Application (BLA) for biologic medicines and maintenance of current Good Manufacturing Practices (cGMPs) for biopharmaceutical manufacturing, the closed U.S. prescription drug distribution system: (1) helps provide assurances regarding the quality, safety and integrity of the products lawfully sold in the U.S.; (2) helps reduce the potential for diversion from the regulated supply chain; and (3) minimizes the risks that a consumer receives a counterfeit medicine. Our prescription drug supply system was closed in 1987 after the passage of the Prescription Drug Marketing Act (PDMA), championed by Reps. John Dingell and Henry Waxman.

A drug is restricted by FDA to prescription use only after it concludes that the medicine may only be used safely under the professional supervision of a practitioner licensed by law to administer such drug. In the U.S., prescription medicines, including controlled substances, typically are sold by a manufacturer to a wholesale distributor, who may in turn sell the product to one or more wholesale distributors, then to an independent or chain pharmacy, at which point the medicine may be dispensed to a patient upon the pharmacy's receipt of a physician prescription for an individual patient. Each of these actors in the supply chain are separate legal entities who take ownership of the medicine as it travels through the supply chain until it is dispensed to a patient, and they are licensed and overseen by the relevant state licensing authority. Further, a patient may not legally obtain a prescription medicine, including a controlled substance, without a prescription from a health care practitioner authorized to write a prescription. Thus, each entity in the prescription drug supply chain – from primary and secondary wholesalers, to licensed pharmacists working in licensed independent and chain pharmacies, to physicians and other licensed health care prescribers – must do their part to help prevent the diversion of medicines to help prevent inappropriate use or misuse. The responsibility to prevent diversion must be equally shared.

Many stakeholders focus on the use of electronic technologies such as pedigree or track and trace systems to help secure our finished product supply chain and to electronically track products from the manufacturer through each change of ownership to the final point at which a medicine is dispensed to patients. We are concerned about the possibility of a patchwork of potentially conflicting state laws addressing pedigree systems. Thus, we believe that a uniform national approach to any electronic

system to track finished prescription drugs in the regulated pharmaceutical distribution chain is of primary importance.

We currently are actively engaged in a coalition effort known as the Pharmaceutical Distribution Security Alliance (PDSA). This effort includes representation from every sector in the finished product distribution chain – manufacturers (brand and generic), wholesalers (primary and secondary), and pharmacies (chain and independent). We remain committed to working with that group to help develop a potential solution to a complex technological and operational issue for the prescription drug supply chain overall. While electronic systems or technologies may serve a deterrent effect, there is no one single technology or electronic system that would be a "silver bullet" to prevent counterfeiting or diversion from the regulated supply chain. The PDSA has developed legislative specifications addressing increasing licensure requirements for wholesale distributors, increasing criminal penalties for counterfeit drugs, enacting controls over online drug sellers, and establishing the building blocks for an electronic tracking system for finished prescription drugs, all of which could help enhance patient safety by minimizing the risk of a patient receiving a counterfeit or diverted prescription drug product, and we remain supportive of their efforts.

Mr. PITTS. That concludes panel two. Thank you very much for your testimony, and we appreciate your patience.

We will now go to panel three, and I would like to call them to the witness table, and I would like to thank all of you for agreeing to testifying before the subcommittee today, and I will quickly introduce our final panel.

First of all, Mr. Shawn Brown is the Vice President of State Government Affairs at the Generic Pharmaceutical Association. Then we have Ms. Elizabeth Gallenagh, who is the Vice President of Government Affairs and General Counsel for the Healthcare Distribution Management Association. And Mr. Tim Davis, who is the Owner of the Beaver Health Mart Pharmacy and representing the National Community Pharmacists Association. And Mr. Allan Coukell, the Director of Medical Programs at the Pew Health Group.

Again, we thank all of you for coming. We have your prepared statements. Mr. Brown, we will begin with you. You are recognized for 5 minutes to summarize your testimony.

STATEMENTS OF SHAWN M. BROWN, VICE PRESIDENT, STATE GOVERNMENT AFFAIRS, GENERIC PHARMACEUTICAL ASSOCIATION; ELIZABETH A. GALLENAGH, VICE PRESIDENT, GOVERNMENT AFFAIRS, AND GENERAL COUNSEL, HEALTHCARE DISTRIBUTION MANAGEMENT ASSOCIATION; TIMOTHY DAVIS, OWNER, BEAVER HEALTH MART PHARMACY, ON BEHALF OF NATIONAL COMMUNITY PHARMACISTS ASSOCIATION; AND ALLAN COUKELL, DIRECTOR, MEDICAL PROGRAMS, PEW HEALTH GROUP, THE PEW CHARITABLE TRUSTS

STATEMENT OF SHAWN M. BROWN

Mr. BROWN. Good morning, Chairman Pitts, Ranking Member Pallone and members of the House Energy and Commerce Subcommittee on Health. Thank you for inviting me to testify before the subcommittee on the important topic of securing our Nation's pharmaceutical supply chain.

I am Shawn Brown, Vice President of State Affairs at the Generic Pharmaceutical Association. GPhA represents the manufacturers and distributors of finished does generic pharmaceuticals and suppliers of other goods and services to the generic industry. We appreciate the efforts of members of this committee particularly Congressmen Matheson and Bilbray, to address this important issue and we share their goal of ensuring the security of our supply chain.

For many years, GPhA had worked closely with multiple stakeholders across the supply chain to ensure U.S. consumers benefit from the safest and most secure prescription drug supply in the world. Both industry and FDA are exceptionally vigilant against the distribution and sale of counterfeit and adulterated medicines.

GPhA believes the problem of counterfeit medicines raises a significant public health concern that must be addressed on a range of levels from local to global and throughout the drug supply chain. Our commitment to this issue is further evidence by the Generic Drug User Fee Act, which recognizes that while providing earlier

access to effective medicines is critical, FDA's central mission is ensuring drug safety. It is worth noting that generic drugs are rarely, if ever, targeted by counterfeiters. The primary focus of counterfeiters is on more profitable and expensive brand name products. GPhA is not aware of a single instance of a counterfeit generic product occurring within the normal chain of distribution in the United States.

Nevertheless, the generic industry has been a leader in supporting numerous anti-counterfeiting efforts and developing methods to further protect the integrity of the pharmaceutical supply chain. As these efforts move forward, however, it is vital to ensure that any system is practical, focused and uniform across the country. The uniform system, founded on reliable technology and business practices, would avoid creating cost barriers to the distribution of safe and effective medicines.

For example, some anti-counterfeiting efforts such as the California model taking effect in 2015 would require implementation of full unit-level track and trace capabilities where theoretically the entire distribution history and location of every unit in the supply chain can be determined at any time. GPhA believes that adoption of the California model or a similar one would raise the cost of medicine by billions of dollars over time, would be prone to error, and would have at best similar results to the less expensive, more efficient model that we support.

With billions of units moving quickly and efficiently through the supply chain to fill more than 4 billion prescriptions per year, the magnitude and complexity of such a system is not technically feasible. The California law does include language providing for preemption of its requirements in the event that Federal legislation is enacted. With California's initial effectiveness date fast approaching, GPhA has helped lead an effort to develop a more efficient model.

In partnership with stakeholders from every area of the pharmaceutical supply chain, the Pharmaceutical Distribution Security Alliance, or PDSA, has developed a consensus technological model that we believe will deliver greater patient safety and help to achieve FDA's stated goals for a supply chain security system.

The PDSA is a multi-stakeholder initiative whose membership spans the U.S. pharmaceutical distribution system including manufacturers, wholesale distributors, third-party logistics providers, and pharmacies. As a member of the PDSA, GPhA strongly supports the alliance's proposed electronic traceability system, known as the Pharmaceutical Traceability Enhancement code, or RxTEC. This system would increase patient access to safe medicines while improving the security of our country's drug distribution system. In addition, the RxTEC system would aid State and Federal agencies in tracing the distribution history of suspect products, replace the inconsistent and inefficient patchwork of State laws, increased efficiency throughout the drug distribution system, and establish foundational technology for future enhancements.

The PDSA model is based on technological solutions that are achievable and scaleable, and unlike a full track and trace system, which is not technically feasible in the near term, the RxTEC system would provide immediate measures to increase supply chain

security. The legislation would provide regulators with new authorities to establish new penalties to address counterfeit products, cargo theft and illegal online drug sellers and create new rules regarding e-labeling that will increase patient safety. It would also improve the efficiency and effectiveness of drug recalls and returns, and enable health care providers to leverage technology for record-keeping purposes. We urge the inclusion of the proposal in the user fee package to accomplish these goals.

In conclusion, Mr. Chairman, GPhA and the industry share the concerns of the committee with regard to maintaining the security of our drug supply and preventing the entry of counterfeit, diverted, stolen or other substandard medicines. The development of a uniform national system is needed to give regulatory authorities another tool for enforcement, make it more difficult for criminals to breach the supply chain, and enhance the ability of the supply chain to respond quickly when a breach has occurred. We believe the RxTEC model proposed by the PDSA achieves all of these goals

Thank you, and I would be happy to answer any questions.

[The prepared statement of Mr. Brown follows:]

SUMMARY OF THE GENERIC PHARMACEUTICAL ASSOCIATION TESTIMONY
BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH
UNITED STATES HOUSE OF REPRESENTATIVES – MARCH 8, 2012
"FDA USER FEES 2012: HEARING ON ISSUES RELATED TO ACCELERATED APPROVAL, MEDICAL GAS, ANTIBIOTIC DEVELOPMENT AND DOWNSTREAM PHARMACEUTICAL SUPPLY CHAIN"

I am Shawn Brown, Vice President of State Affairs at the Generic Pharmaceutical Association. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, bulk pharmaceutical chemicals, and suppliers to the generic industry. Generic pharmaceuticals fill 80 percent of the prescriptions dispensed in the U.S. but consume just 25 percent of the total drug spending.

For many years, GPhA has worked closely with multiple stakeholders across the supply chain to ensure that U.S. consumers will continue to benefit from the safest and most secure prescription drug supply chain in the world. Our commitment to this issue is evidenced by the historic Generic Drug User Fee Act currently being considered by the Committee, under which FDA will receive $1.5 billion over five years from the generic industry, which will hold all players contributing to the U.S. generic drug system, foreign or domestic, to the same inspection standards. As the Committee further considers downstream pharmaceutical supply chain issues, it is vital to ensure that any national system developed is practical, focused, and uniform across the country.

Previous Efforts to Regulate the Pharmaceutical Supply Chain
Several Members of Congress have introduced legislation in recent years that would urge the establishment of national standards for an electronic prescription drug tracking system, and we look forward to working with them to achieve our shared goal of ensuring the safety of the U.S. drug supply. On the state level, California has passed a law requiring manufacturers to implement a unit-level, interoperable electronic track-and-trace system. GPhA believes that adoption of the California model will cost the industry billions of dollars over time, would be prone to error, and would have, at best, similar results to the less-expensive, more efficient model we propose. GPhA has helped lead an effort to develop an alternative approach to increase the security of the U.S. drug supply.

The PDSA Model
The Pharmaceutical Distribution Security Alliance (PDSA) is a multi-stakeholder initiative whose membership spans the U.S. pharmaceutical distribution system, including manufacturers, wholesale distributors, third-party logistics providers and pharmacies. PDSA's mission is to develop a federal policy that enhances the security and integrity of the domestic pharmaceutical distribution system for patients and ensure patients have uninterrupted access to safe, authentic, FDA-approved medicine.

As a member of PDSA, GPhA strongly supports the Alliance's proposed electronic traceability system known as the Pharmaceutical Traceability Enhancement Code (RxTEC), which would increase patient access to safe medicines while improving the security of our country's drug distribution system. The RxTEC system would aid state and federal agencies in tracing the distribution history of suspect products, replace the inconsistent and inefficient patchwork of state laws, increase efficiency throughout the drug distribution system, and establish foundational technology for future enhancements.

As part of the RxTEC system, manufacturers have committed to serializing individual saleable units of medicine and maintaining and managing data in their systems that would associate the serial numbers on individual bottles of medicine with the lot numbers of products. This system would help identify and prevent the introduction of suspect product through full lot traceability and allow regulatory authorities to validate the serial number of a product at the unit level. And unlike a full track-and-trace system, which is not technologically feasible in the near term, the RxTEC system would provide immediate measures to increase supply chain security.

The system would additionally provide regulators with new authorities and penalties to address counterfeit products, cargo theft, illegal online drug sellers, and new rules regarding e-labeling that will increase patient safety. It would also create more stringent federal standards and state licensing for wholesale distributors.

TESTIMONY OF SHAWN M. BROWN

VICE PRESIDENT OF STATE AFFAIRS

GENERIC PHARMACEUTICAL ASSOCIATION

"FDA USER FEES 2012: HEARING ON ISSUES RELATED TO ACCELERATED APPROVAL, MEDICAL GAS, ANTIBIOTIC DEVELOPMENT AND DOWNSTREAM PHARMACEUTICAL SUPPLY CHAIN"

BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

MARCH 8, 2012

Good morning Chairman Pitts, Ranking Member Pallone and Members of the House Energy and Commerce Subcommittee on Health. Thank you for inviting me to testify before the subcommittee on the important topic of securing our nation's pharmaceutical supply chain.

I am Shawn Brown, Vice President of State Affairs at the Generic Pharmaceutical Association. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, bulk pharmaceuticals and suppliers of other goods and services to the generic industry. Generic pharmaceuticals now fill 80 percent of all prescriptions dispensed in the U.S., but account for only 25 percent of the total 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 and $158 billion in 2010 alone — which equates to $3 billion in savings every week. The quality and affordability of generic medicines is vital to public health and the sustainability of the health care system.

Introduction

For many years, GPhA has worked closely with multiple stakeholders across the supply chain to ensure that U.S. consumers will continue to benefit from the safest and most secure prescription drug supply in the world. Both industry and the FDA are

exceptionally vigilant against the distribution and sale of counterfeit and adulterated medicines.

Any presence of counterfeit and adulterated pharmaceuticals in our supply chain threatens the integrity of our industry and, more importantly, the health of patients. As the makers of 80 percent of the prescriptions dispensed in the U.S., the generic pharmaceutical industry is deeply committed to ensuring the security of our country's drug supply. GPhA believes that the problem of counterfeit medicines raises a significant public health concern that must be addressed systemically on a range of levels — from local to global, and throughout the drug supply chain.

Our commitment to this issue is further evidenced by the historic Generic Drug User Fee Act currently being considered by the Committee, which recognizes that while providing earlier access to effective medicines is critical — and the key aim of all other existing user fee programs —FDA's central mission is ensuring drug safety. The overall goal of the program is to hold all players, foreign or domestic, contributing to the U.S. generic drug system to the same Good Manufacturing Practices (GMP), and inspection standards, while expediting access to more affordable, high quality generic drugs; the generic drug user fee program will also enhance FDA's ability to identify, track and require the registration of all contributors involved in each generic drug product sold in the U.S.

It is worth noting that low-cost generic drugs are rarely, if ever, targeted by counterfeiters. The primary focus of counterfeiters is on more profitable, and expensive, brand-name products. And in general, as the FDA acknowledges, "counterfeiting is quite rare within the U.S. drug distribution system." GPhA is not aware of a single instance of a counterfeit generic product occurring within the normal chain of distribution in the US. Nevertheless, the generic industry has been a leader in supporting numerous anti-counterfeiting efforts and developing methods to further protect the integrity of the pharmaceutical supply chain. The generic industry is committed to ensuring the safety of the millions of consumers nationwide who use safe, affordable generic medications.

As these efforts move forward, however, it is vital to ensure that any system is practical, focused, and uniform across the country. A uniform system founded on reliable technology and business practices would preclude the unintended consequence of erecting cost barriers to the distribution of safe and effective medicines.

For example, some anti-counterfeiting efforts, such as the drug pedigree model currently set to take effect in 2015 under California law, would require implementation of full electronic "track and trace" capabilities, where the entire distribution history, and the location, of every unit in the supply chain can be determined at any time. The technology to support such a system is unreliable, underdeveloped and the costs associated with such a model would be enormous. Considering the myriad of manufacturers, packaging operations and potential exceptions, this is not a realistic

expectation. Additionally, the California law does not require the Standardized Numerical Identifier (SNI) to be used to verify authenticity, only that there is a pedigree for each number. Drug pedigrees have been forged. An attempt to implement such a system would lead to confusion in the supply chain, aggravate product shortages and dramatically increase costs. Such costly measures would significantly impact the costs for all prescriptions, including low-cost generic medicines.

Previous Efforts to Regulate the Pharmaceutical Supply Chain

As the Committee begins to look closer at this important issue, it is critical to understand how previous efforts at regulating the pharmaceutical supply chain — at both the state and federal level — have led us to where we stand today.

In 1988, Congress passed the Prescription Drug Marketing Act, or PDMA, requiring drugs to be tracked when they passed outside of the normal chain of distribution, which begins at the manufacturer, goes to authorized distributors and finally to the pharmacy. Congress found this necessary because the majority of drugs that were counterfeit, stolen, expired or obtained through fraud were handled by secondary wholesalers, who were not authorized to distribute a manufacturer's product. Manufacturers and their authorized distributors were exempted from these requirements, because the introduction of counterfeit medicines would rarely, if ever, occur in this link of the supply chain. However, the law was stayed by the FDA, and finally enjoined in 2006 by a federal district court in New York, in large part because the creation of a national drug

tracking system including all supply chain participants had not been mandated, making the requirements potentially too difficult or impossible to fulfill for many legitimate distributors.

Since that time, this Committee and the Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA), which directs the FDA to develop standards for the identification, validation, authentication and tracking of prescription drugs, as well as a standard numerical identifier to be applied to a prescription drug at the point of manufacturing and repackaging. While most of these standards have yet to be established, the FDA envisions a full track-and-trace system similar to that in California. However, the FDA concept would require that aggregation of serial numbers — establishing and maintaining that the relationship between unit-level serial numbers with case and pallet serial numbers —be 100 percent accurate. This cannot be achieved. GPhA believes that, in these efforts, perfection has been the enemy of good.

Additional federal legislation has also been introduced in recent years that would urge the establishment of national standards for an electronic tracking system. The legislation pursues the worthy goal of a single, uniform national standard for supply chain security, as opposed to a patchwork of differing state-by-state laws. However, the measures proposed would ultimately require an extensive track-and-trace model for each individual saleable unit of medicine. GPhA believes that adoption of the California model, or one with very similar features, would raise the cost of medicine by billions of dollars over time, would be prone to error, and would have, at best, similar results to the

less-expensive, more efficient model we propose. With billions of units moving quickly and efficiently through the supply chain to fill more than 4 billion prescriptions per year, the magnitude and complexity of such a system is not technically feasible. Indeed, all have underestimated the complexity of the technology requirements and changes in business practices, except those that will use the system every day. Nevertheless, we appreciate the efforts of Members of this Committee to address this important issue and share their goal of ensuring the security of the U.S. pharmaceutical supply chain. Namely, we recognize and appreciate the dedicated attention to this issue given by Congressman Matheson and Congressman Bilbray.

The California law does include language providing for preemption of its requirements in the event that federal legislation is enacted. It is just such an achievement that the Pharmaceutical Distribution Security Alliance (PDSA) hopes this committee will support. With California's initial effectiveness date of 2015 fast approaching, GPhA has helped lead an effort to develop a better approach. In partnership with stakeholders from every area of the pharmaceutical supply chain, we have developed a consensus technological model for increasing the security of the drug supply chain in the U.S. that, we believe, will deliver greater patient safety and help to achieve the FDA's stated goals of preventing the introduction — and facilitating the identification — of counterfeit, diverted, sub-potent, substandard, adulterated, misbranded or expired drugs, providing accountability for the movement of drugs by supply chain participants, and improving the efficiency and effectiveness of recalls. Let me provide some more details.

The PDSA Model

The Pharmaceutical Distribution Security Alliance, or PDSA, is a multi-stakeholder and interdisciplinary initiative whose membership spans the entire spectrum of the U.S. pharmaceutical distribution system, including manufacturers, wholesale distributors, third-party logistics providers and pharmacies.

The PDSA's mission is to develop, and help enact, a federal policy proposal that enhances the security and integrity of the domestic pharmaceutical distribution system for patients, and to articulate a technical migratory pathway to implement such a policy. Our primary goal is to ensure patients have uninterrupted access to safe, authentic, FDA-approved medicine.

As a member of the PDSA, GPhA strongly supports the Alliance's proposed electronic traceability system known as the Pharmaceutical Traceability Enhancement Code, or RxTEC. This system would increase patient access to safe medicines, while improving the security of our country's drug distribution system. In addition, the RxTEC system would aid state and federal agencies in tracing the distribution history of suspect products, replace the inconsistent and inefficient patchwork of state laws, increase efficiency throughout the drug distribution system and establish foundational technology for future enhancements. The PDSA model is based on technology that we are certain is achievable and scalable.

Specifically, as part of the RxTEC system, manufacturers have committed to serializing individual saleable units of medicine with RxTEC labels, and maintaining and managing RxTEC data in their systems that would associate the serial numbers on individual bottles of medicine with the lot numbers of products. Further, RxTEC peer-to-peer communications would contain the quantity of units associated with the lot. Unit-level serialization provides greater granularity of a lot and improves the visibility of its distribution throughout the supply chain, and also provides unit-level data as an additional check. This system would help identify and prevent the introduction of suspect product through full lot traceability and allow regulatory authorities to validate the serial number of a product at the unit level.

And unlike a full track-and-trace system, which is not technologically feasible in the near term, the RxTEC system would provide immediate measures to increase supply chain security. The system would provide regulators with new authorities and penalties to address counterfeit products, cargo theft, illegal online drug sellers, and new rules regarding e-labeling that will increase patient safety. It would also create more stringent federal standards and state licensing for wholesale distributors, and streamline requirements for manufacturers who also operate as distributors.

To increase the proficiency of the drug distribution system, the RxTEC system would also improve the efficiency and effectiveness of drug recalls and returns, and enable health care providers to leverage technology for record keeping purposes. And in planning for the future, it would provide critical building blocks that can be expanded as

public health threats, interoperability standards and technologies evolve, and establish connectivity and infrastructure throughout the supply chain that will enable a variety of other capabilities and efficiencies.

In short, the RxTEC system is a national supply chain stakeholder consensus model that will replace the patchwork of inconsistent state laws, while increasing patient safety and enhancing our ability to identify and prevent the introduction of suspect product. It is important to recognize the limitations of technology and the necessity of other means of vigilance to address the issues of counterfeiting and diversion of drugs. There is no technology or tracking system that will stop thieves and counterfeiters from attempting to divert products, or profit illegally. However, the PDSA's legislative model represents a landmark improvement in the safety and security of the supply chain, not only through serialization technology to support lot traceability, but also through new stricter licensing requirements, new regulatory authorities, new labeling features and stronger penalties for criminals. We urge the inclusion of the proposal in the user fee package to accomplish these goals.

Conclusion

In conclusion, Mr. Chairman, GPhA and the industry share the concerns of the Committee with regard to maintaining the security of our country's drug supply and preventing the entry of counterfeit, diverted, stolen or other substandard medicines. The development of a uniform, national system is needed to give regulatory authorities

another tool for enforcement, make it more difficult for criminals to breach the supply chain and enhance the ability of the supply chain to respond quickly when a breach has occurred. We believe the RxTEC model proposed by the PDSA achieves all of these goals. Thank you and I would happy to answer any questions you may have.

Mr. PITTS. The Chair thanks the gentleman.

Ms. Gallenagh, you are recognized for 5 minutes.

STATEMENT OF ELIZABETH A. GALLENAGH

Ms. GALLENAGH. Good afternoon, Chairman Pitts, Ranking Member Pallone and members of the Subcommittee on Health, I am Liz Gallenagh, Vice President of Government Affairs and General Counsel at HDMA. Thank you for the opportunity to inform the subcommittee today regarding this critically important issue of prescription drug pedigree, traceability and pharmaceutical supply chain safety. I would also like to thank Congressmen Bilbray and Matheson for their bipartisan leadership in this area.

The pharmaceutical distribution industry's primary mission is to operate the safest, most secure and efficient supply chain in the world. As part of this mission, HDMA's members work to eliminate counterfeit and diverted medicines by capitalizing on the technological innovation and constant improvements in efficiency that are the foundation of our industry.

Today, I am here to express HDMA's strong support for a national uniform approach to pedigree and the traceability of medicines throughout the supply chain. HDMA believes that reform should have tighter wholesaler licensing standards and a new Federal ceiling for pedigree requirements to improve safety and uniformity across the country while establishing targets and parameters for longer-term electronic traceability solutions.

In addition to fundamentally addressing counterfeit and diverted medicines, we also believe that Federal pedigree may have some potential as a useful tool in discouraging gray-market activity associated with drug products in short supply. After many years of debate, 2012 is the best window of opportunity to enact national pedigree legislation. This is in large part due to broad consensus among supply chain partners as well as the possibility of attaching national pedigree and traceability provisions to PDUFA reauthorization.

Basic guidelines for pedigree were set forth nearly 25 years ago with the enactment of the Federal PDMA. Since that time, activity at the State level has varied with some enacting complex electronic pedigree laws and other never going further than the original 1988 guidelines. Based on our experience, the complexities of dealing with multiple approaches in the States will only get worse if we fail to solve this problem now at the national level.

Since Florida's first foray in raising pedigree and licensure requirements in 2003, we have seen dramatic variation across the country in both legislation activity and regulatory interpretation. This has occurred despite our attempts to work in every State along with our fellow stakeholders and interested legislators to achieve more uniformity. Today, for example, 29 States have acted beyond the Federal PDMA standards. For instance, the States of California and Florida are thought to be the most stringent and leaders in this area. However, they take completely different viewpoints with Florida considered to the most stringent today and California thought to be the most complex in the future in 2015 when their law is implemented.

This patchwork not only creates operational challenges but also creates openings for bad actors to shop for more lenient States rules, openings that could mean the difference between a fake or diverted medicine being dispensed or administered to an innocent patient in need of treatment. Because of this State-by-State variation, we believe that pedigree and traceability should be under the purview of Congress and the FDA.

HDMA is currently a part of an industry alliance, a consortium of other industry partners called the PDSA. PDSA's consensus model calls for the following: national requirements for wholesaler licensing standards and for direct purchase and standard pedigree upon the effective date of the legislation; manufacturer serialization at the unit and case levels, enabling unique identification of prescription drug products for the first time; the development of electronic systems to facilitate traceability and transaction data exchange to provide additional efficiency and safety benefits within the supply chain; appropriate transition time and development phases for the migration to traceability for each segment of the supply chain. Further, Federal legislation must also preserve the critically important role of the States, for instance, in the area of wholesaler licensure and enforcement. There is no single element that will protect the supply chain from every threat but rather a comprehensive solution should incorporate each of these elements.

We urge the subcommittee to consider this important issue for inclusion in PDUFA legislation. Now is the time for Congress to act to bring cohesion and consistency to our national drug supply chain. Thank you.

[The prepared statement of Ms. Gallenagh follows:]

HDMA Testimony

Statement from
Elizabeth A. Gallenagh, Vice President
Government Affairs and General Counsel
Healthcare Distribution Management Association

For the U.S. House of Representatives
Energy and Commerce Committee
Subcommittee on Health

March 8, 2012

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HDMA
Healthcare Distribution Management Association

Good morning Chairman Pitts, Ranking Member Pallone and Members of the Energy and Commerce Subcommittee on Health. I am Elizabeth Gallenagh, Vice President, Government Affairs and General Counsel of the Healthcare Distribution Management Association (HDMA). Thank you for the opportunity to inform the Subcommittee regarding the critically important issue of prescription drug pedigree and pharmaceutical supply chain safety. I would also like to thank Congressmen Bilbray and Matheson for their leadership in this area.

HDMA represents the nation's primary pharmaceutical distributors that purchase prescription drugs and other healthcare products from manufacturers and deliver them every day to 200,000 pharmacy and provider settings across the country.

Our 34 member companies are responsible for storing, managing and delivering nearly 90 percent of all prescription medicines sold in the U.S. This critical public health function is performed with tremendous efficiency, saving the nation's healthcare system nearly $42 billion each year.

The pharmaceutical distribution industry's primary mission is to operate the safest, most secure and efficient supply chain in the world. As part of this mission, HDMA's members work to eliminate counterfeit and

diverted medicines by capitalizing on the technological innovation and constant improvements in efficiency that are the foundation of our industry.

Today, I am here to express HDMA's strong support for a national, uniform approach to the pedigree and traceability of medicines throughout the supply chain. HDMA believes that reform should have tighter wholesaler licensing standards and a new federal ceiling for traceability requirements to improve safety and uniformity across the country, while establishing targets and parameters for longer-term electronic solutions. In addition to fundamentally addressing counterfeit and diverted medicines, federal pedigree may be a useful tool in discouraging gray market activities associated with drug products in short supply.

After many years of debate, 2012 is the best window of opportunity to enact federal pedigree legislation. This is, in large part, due to a broad consensus among supply chain partners as well as the possibility of attaching a federal pedigree provision to the Prescription Drug User Fee Act (PDUFA) reauthorization.

Because of the unique role HDMA members play in the supply chain between manufacturers and providers, including pharmacies, they see firsthand the complexities of dealing with the current 50-state wholesaler

licensing and pedigree laws (see attached map of state pedigree legislation and regulations).

Basic guidelines for pedigree were set forth nearly 25 years ago with the enactment of the federal Prescription Drug Marketing Act (PDMA). Since that time, activity at the state level has varied with some enacting complex electronic pedigree laws and others never going further than the original 1988 guidelines. Based on our experience, the complexities of dealing with multiple approaches in the states will only get worse if we fail to solve this problem at the federal level.

Since Florida's first foray into raising pedigree and licensure requirements in 2003, we have seen dramatic variations across the country in both legislative activity and regulatory interpretation. This variation has occurred despite HDMA's attempts to work in every state along with fellow stakeholders and interested legislators and regulators to achieve more uniformity. Today, for example, 29 states have acted beyond the federal PDMA standards. The states of Florida and California are viewed as leaders in this arena. However, they take completely different approaches with Florida considered to be the most stringent in terms of today's requirements and California the most complex once its electronic pedigree law is implemented in 2015.

This patchwork not only creates operational challenges, but also creates openings for bad actors to shop around for more lenient state rules — openings that could mean the difference between a fake or diverted medicine being dispensed or administered to an innocent patient in need of treatment. Because of this state-by-state variation, we believe that pedigree and traceability should be under the purview of Congress and the FDA.

HDMA has been a leader in this area, forming and participating in industry task forces and working groups that bring together manufacturers, distributors and pharmacies dedicated to identifying the operational and technical requirements for electronic pedigree, track-and-trace and traceability implementation. We are currently part of an industry alliance, the Pharmaceutical Distribution Security Alliance (PDSA), which is dedicated to working on a consensus approach to pharmaceutical traceability. PDSA has developed a consensus model that includes support from manufacturer, distributor and pharmacy stakeholders.

This comprehensive, practical approach would result in increased safety, continued efficiencies and minimal inconsistencies among competing state requirements — all of which will enable HDMA distributors

and our supply chain partners to continue to deliver prescription drugs safely and efficiently every day.

This consensus model includes:

- National Uniformity

  Adoption of national requirements for wholesaler licensing standards and for direct-purchase and standard pedigree (documentation of product distribution history) upon the effective date of the legislation (or shortly thereafter). Taking this immediate first step would help to ensure the efficient flow of prescription drugs between states, raise the bar for states that have not gone beyond the current federal PDMA "floor" and enhance protection for the most secure prescription drug supply chain in the world — further ensuring patient safety and just-in-time access to lifesaving medicines.

- Unit-level Serialization

  Currently, there is no mechanism required to identify a unique bottle of medicine. This proposal would require manufacturers to apply a unique identifier to prescription drugs at the unit and case levels. This would be the first in a series of steps designed to help protect the supply chain against counterfeit, adulterated or other substandard

product by facilitating improved ability to identify non-legitimate products. Products would be identified at the unit and case level with GTIN and serial number (SNI), lot number and expiration date for the product. (This is referred to as "RxTEC".)

- Data Exchange and Systems Development

  Once product is serialized, it is believed that product traceability initially can be achieved at the lot level, with potential for traceability at more discrete levels as systems mature. As a result, exchange of transaction data will be possible and can be leveraged to provide additional efficiency and safety benefits within the supply chain. HDMA supports a path toward traceability that includes deliberate, careful evaluation and assessment by FDA and stakeholders at each step.

- Prescription Drug Traceability

  A migration to traceability must include appropriate transition time and development phases for each segment of the supply chain. Further use of product information should be determined based on the current state of industry, proven technologies, as well as potential to enhance patient safety.

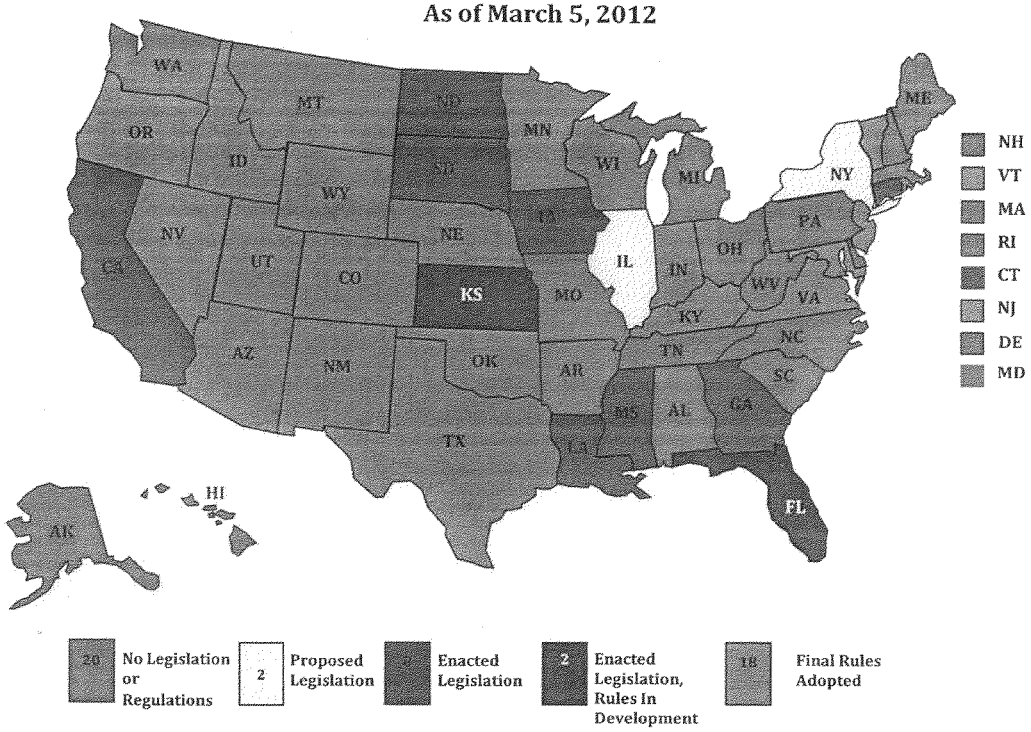
Federal legislation must preserve the critically important role for states to license and enforce. There is no single element that will protect the supply chain from every threat but rather, a comprehensive solution should incorporate each of the elements above.

We urge the Subcommittee to consider this important issue for inclusion in the PDUFA legislation. The integrity of the supply chain is dependent on commitment and participation by all supply chain partners and any workable solution must include manufacturers, distributors, pharmacies and other healthcare providers who dispense medications. Now is the time for Congress to act to bring cohesion and consistency to our national drug supply chain.

Thank you.

2012 HDMA Map of State Pedigree Legislation/Regulations

As of March 5, 2012



Mr. PITTS. The Chair thanks the gentlelady.

Dr. Davis, you are recognized for 5 minutes.

STATEMENT OF TIMOTHY DAVIS

Mr. DAVIS. Chairman Pitts, Ranking Member Pallone and members of the subcommittee, thank you for conducting this hearing and providing me an opportunity to share my views and my perspective as an independent pharmacist on the issue of securing the pharmaceutical supply chain.

My name is Tim Davis of Beaver County, Pennsylvania, and I own the Beaver Health Mart Pharmacy in that town and county. I have been a practicing pharmacist for 12 years, and I am here today representing the National Community Pharmacists Association. It is an association of over 23,000 independent pharmacists, and we are the pharmacists that represent over 40 percent of the prescriptions dispensed in this country.

It is my belief that the pharmaceutical supply chain in the United States is largely safe and secure. I believe that today most practicing pharmacists have a heightened awareness of the possibility of counterfeit or diverted drugs and therefore recognize the critical importance of purchasing medications only from trusted wholesalers or trading partners. In addition, most pharmacists today make a concerted effort to carefully examine and make note of drug packaging and the appearance of the drug itself to make sure that there are no suspicious anomalies.

It has been my observation that certain types of prescription medications tend to be the target of counterfeiters. High-dollar medications that can be easily produced and readily sold generally enable counterfeiters to create an attractive profit margin. Presently, generics are not typically a target for this type of activity. Some drugs that I have seen are particularly susceptible and are lifestyle drugs such as Viagra, as well as a number of very expensive injectable medications, and most recently, Avastin. These are typically not carried in community pharmacies but rather dispensed through consolidated specialty pharmacies or directly through physicians.

In my career, I have seen an example of counterfeiting at the local level. We received manufacturer information that a particular drug had entered the drug supply chain in counterfeit form, and the manufacturer instructed us on how to recognize the genuine product versus the fake. Upon receipt of a daily shipment in the morning from our wholesale distributor, we checked and found that the item we received was indeed one of the counterfeit products. We immediately contacted and discussed the situation with the wholesaler. Our answer was to stop doing business with them due to lack of believable responses.

That being said, NCPA does believe that there are a number of different approaches or tactics that could be employed to provide further confirmation of integrity. These strategies could include national uniform Federal licensure standards for wholesale distributors, increased oversight or security measures to deter pharmaceutical cargo theft and illegitimate online drug sellers, and lot-level form of tracking for prescription drugs to assist the FDA or

State authorities in the event of recall or to investigate suspect product.

Raising the standards for wholesaler licensure in a uniform fashion would provide the community pharmacist at any location in the United States with an additional layer of confidence in the integrity of the medications purchased from such companies. Therefore, NCPA recommends that the U.S. government set national uniform and Federal licensure standards for wholesale distributors. At the present time, these distributors are licensed at the individual State level, which has resulted in a patchwork of requirements of varying rigor.

There are a number of other approaches that could also further secure the pharmaceutical supply chain. S. 1002, the SAFE DOSES Act, would expand the penalties for pharmaceutical cargo theft, and in addition, H.R. 4095, the Online Pharmacy Safety Act, would create a publicly available white list of legitimate Internet pharmacies. This list would help to eliminate rogue Internet pharmacies that exist and often prey on consumers looking for bargain-priced medications.

NCPA is a member of the Pharmaceutical Distribution Security Alliance, a working group comprised of representatives from all sectors of the pharmaceutical supply chain. It has been collaborating on a comprehensive proposal to address supply chain security issues. The RxTEC Act is currently in draft form. However, it includes language that would create the registry of legitimate online pharmacy Web sites, increase the penalties for counterfeiters as well as provide for tracking of prescription medications at the lot level.

The actual tracking of prescription drugs through the supply chain is a topic that has been discussed for a number of years, and independent community pharmacists have had significant concerns in the past about the cost of the hardware, software and employment burdens placed upon the association. This is a complex issue both in terms of the technologies necessary to implement it as well as the fact that each of the sectors involved in the supply chain operate under very different business models and very greatly in terms of financial resources and technological sophistication. Community pharmacies are largely small businesses. Any system that would require a pharmacist to electronically scan each item would create a burdensome and time-consuming exercise that would further limit the amount of time that we have to provide patient care and counseling or any other activities necessary to keep that small business running.

The tracking system proposed under RxTEC Act is one that is lot-based tracking, would require that the encoded information on each unit be both machine and human readable, and would allow for collaboration between all members of the supply chain. The proposed system is one that could be built upon in the future if it was determined that this course of action was advisable but is one that would not impose an undue burden either financially or as it relates to work flow upon independent community pharmacists.

I have a greater degree of confidence in the United States drug supply than I did just a few years ago, largely due to heightened awareness of those in the supply chain and the possibility of coun-

terfeit or diverted medications being discovered. That being said, community pharmacies take very seriously our role in ensuring the safety of medications that we personally dispense to our patients and we remain committed to working with our colleagues in the supply chain, other pharmacy organizations, wholesalers and manufacturers as well as with State and Federal authorities to make any needed improvements. Moving forward, it is essential that all stakeholders make a concerted effort to keep the lines of communication open so that consumers can continue to implicitly trust the integrity of the medications that they depend on.

I thank you, and welcome any questions.

[The prepared statement of Mr. Davis follows:]

Timothy Davis, Pharm.D.
National Community Pharmacists Association
Summary of Statement
Before
United States House of Representatives Energy and Commerce Committee
Subcommittee on Health
Hearing on
FDA User Fees 2012: Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain
March 8, 2012

NCPA appreciates the opportunity to share the community pharmacy perspective on issues relating to securing the pharmaceutical supply chain. NCPA represents America's community pharmacists, including the owners of more than 23,000 community pharmacies, pharmacy franchises and chains.

National, Uniform Federal License Standards for Wholesale Distributors and Logistics Providers
NCPA recommends the development of national, uniform, federal license standards for wholesale distributors and logistics providers (3PLs). At present, wholesale distributors are licensed at the individual state level, which has resulted in a patchwork of conflicting requirements. By setting a high bar nationwide, we could further safeguard the supply chain by making sure that only appropriately credentialed and legitimate entities are able to participate in the drug distribution aspect of the pharmaceutical supply chain. These new federal standards would preempt existing state requirements.

Other Measures to Secure the Supply Chain
S. 1002, the *Safe Doses Act*, would expand the penalties for pharmaceutical cargo theft. In addition, H.R. 4095, the *Online Pharmacy Safety Act* would create a publicly available "white list" of legitimate internet pharmacies to be managed by the FDA or its contracting organization. This list would help educate consumers and crack down on the "rogue" internet pharmacies that currently exist and are used by consumers looking for "bargain" prescription medications.

Pharmaceutical Distribution Security Alliance and Use of RxTec Act
NCPA is currently a member of the Pharmaceutical Distribution Security Alliance (PDSA), a working group comprised of representatives of all sectors of the pharmaceutical supply chain, which together has worked to develop the RxTec Act. This draft legislation would create a registry of legitimate on-line pharmacy websites, increase penalties for counterfeiters and provide for the tracking of prescription medications at the lot level. Independent community pharmacists have had reservations in the past due to concerns about the cost of the hardware and software that would be required to set up such a system as well as the significant time and labor costs associated with it. The RxTec proposal specifies that the encoded information on each finished prescription drug unit must be in both machine readable and human readable form. The proposal would also enable independent community pharmacists to rely upon the records of their trusted wholesaler if needed to double check the lot numbers in question.

Conclusion
Community pharmacists take seriously our role in ensuring the safety of the medications that we personally dispense to our patients. We remain committed to working with our colleagues in the supply chain—other pharmacy organizations, wholesalers and manufacturers—as well as with state and federal authorities to make any needed improvements. It is essential that all stakeholders make a concerted effort to keep the lines of communication open so that consumers can continue to trust the integrity of the medications that they depend upon.

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

Hearing on FDA User Fees 2012: Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain

Testimony of Timothy Davis, Independent Pharmacist and Member of the National Community Pharmacists Association

March 8, 2012

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee: Thank you for conducting this hearing and for providing me the opportunity to share my views and perspective as an independent pharmacist on the issue of securing the pharmaceutical supply chain.

My name is Tim Davis of Beaver, Pennsylvania. I am the owner of the Beaver Health Mart Pharmacy and have been a practicing pharmacist for twelve years. I am here today representing the National Community Pharmacists Association (NCPA), which represents the pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. These pharmacies provide about 40 percent of all community-based prescriptions.

It is my belief that the current pharmaceutical supply chain in the United States is safe and secure. I believe that today most practicing pharmacists have a heightened awareness of the possibility of counterfeit or diverted drugs in the supply chain, and therefore recognize the critical importance of purchasing medications only from trusted wholesalers or trading partners. In addition, most pharmacists today make a concerted effort to carefully examine and make note of drug packaging and the appearance of the drug itself to be sure that there are no suspicious anomalies.

In the past, it has been my observation that certain types of prescription medications were likely candidates to be the target of counterfeiters or "bad actors" in the supply chain. High dollar medications that can be easily produced and readily sold generally enable counterfeiters to create an attractive profit margin. Low-cost generics are typically not a target for this type of activity, and now almost 80 percent of all prescriptions are dispensed with generics. Some drugs that I have seen that are particularly susceptible are lifestyle drugs, such as Viagra or Cialis, as well as a number of very expensive injectable medications such as Procrit or Lovenox.

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That being said, NCPA does believe that there are a number of different approaches or tactics that could be employed to assure pharmaceutical integrity. These strategies could include national, uniform federal license standards for wholesale distributors and logistics providers, increased oversight or security measures to deter pharmaceutical cargo theft and potentially some form of tracking for prescription drugs.

National, Uniform Federal License Standards for Wholesale Distributors and Logistics Providers

As a result of greater oversight by states of their drug wholesale distributors, many of the bad actor wholesalers have already been eliminated from the marketplace. However, as part of a comprehensive approach to supply chain security, or perhaps as a stand-alone proposal, NCPA recommends that national, uniform, federal license standards for wholesale distributors and logistics providers (3PLs) also be developed. At the present time, wholesale distributors are licensed at the individual state level, which has resulted in a patchwork of conflicting requirements of varying rigor.

By setting a high bar for wholesale distributors nationwide, we could further safeguard the supply chain by making sure that only appropriately credentialed and legitimate entities are able to participate in the drug distribution aspect of the pharmaceutical supply chain. These new federal standards would preempt existing state requirements, although the individual states would still certify compliance with the federal standards and register wholesalers for an appropriate fee.

As I mentioned earlier in my testimony, the relationship between the community pharmacist and his or her wholesaler is one of critical importance. Most independents only purchase from a single primary wholesaler, but they also have other reputable sources of supply if the primary wholesaler doesn't stock or runs out of the product. Raising the standards for wholesaler licensure in a uniform fashion would provide the community pharmacist at any location in the United States with an additional layer of confidence in the integrity of the medications purchased from such companies.

Other Measures to Secure the Supply Chain

There are a number of other related measures that are currently being proposed, both in stand-alone proposals as well as in a number of comprehensive approaches that could also further secure the pharmaceutical supply chain. For example, S. 1002, *The Safe Doses Act*, would expand the penalties for pharmaceutical cargo theft.

In addition, H.R. 4095, the *Online Pharmacy Safety Act* would create a publicly available "white list" of legitimate internet pharmacies to be managed by the FDA or its contracting organization. This list would help educate consumers and crack down on the "rogue" internet pharmacies that currently exist and are used by consumers looking for "bargain" prescription medications.

Pharmaceutical Distribution Security Alliance and Use of RxTec Act

NCPA is currently a member of the Pharmaceutical Distribution Security Alliance (PDSA), a working group comprised of representatives of all sectors of the pharmaceutical supply chain that has been collaborating on a comprehensive proposal to address supply chain security issues. This proposal, the RxTec Act, is currently in draft form; however it includes language that would create a "registry" of legitimate on-line pharmacy websites, increased penalties for counterfeiters as well as the tracking of prescription medications at the lot level.

The tracking of prescription drugs through the supply chain is a topic that has been discussed for a number of years. Independent community pharmacists have had significant reservations in the past due to concerns about the cost of the hardware and software that would be required to set up such a system as well as the significant time and labor costs associated with it. This is a complex issue because of the integrated technologies necessary to implement it. In addition, each of the sectors involved in the supply chain operate under completely different business models and vary greatly in terms of financial resources and technological capabilities and sophistication.

Independent community pharmacies are largely small business owners, many of whom are single store owner or operators. Unlike our chain counterparts, we do not have a "corporate" office to rely upon with regard to operational upgrades or have a surplus of staff. Any system that would require pharmacists to individually "scan" each item would create a burdensome and time consuming exercise that would further limit the amount of time a community pharmacist has to provide actual patient counseling and other activities necessary to keep the pharmacy up and running. For these reasons, NCPA has in the past, and continues to be, opposed to electronic tracking systems that would require the pharmacist to individually "scan" each prescription drug unit that arrives from the wholesaler into a pharmacy's stock.

It is important to note that the implementation of a tracking system would not necessarily alleviate or "fill in" all of the potential gaps in the pharmaceutical supply chain; however, such a system could serve as a useful tool to strengthen the chain and assist in FDA investigations and recalls.

As mentioned earlier, NCPA has been participating in the PDSA coalition and one element of that coalition's proposal provides for the tracking of prescription medications at the lot level. The proposal specifies that the encoded information on each finished prescription drug unit must be in both machine readable and human readable form. The proposal would also enable independent community pharmacists to rely upon the records of their trusted wholesaler if needed and agreed to by both parties, to confirm or double check the lot numbers in question.

Conclusion

On the front lines of patient care, community pharmacists take seriously their responsibility to remain vigilant against counterfeit or diverted drugs. One way that we currently do this is to buy products only from trusted trading partners, remain alert to packaging and medication appearance anomalies, and follow all manufacturer alerts and recalls. Diverted or counterfeit drugs often enter the supply chain as a result of pharmaceutical cargo thefts and illegitimate on-line drug sellers. In addition, under the current laws in effect, counterfeiters stand to reap enormous profits from their illicit activities while the legal penalties associated with the activity are not rigorous enough to serve as any type of deterrent. Any strategy or plan to tighten up the supply chain must be a multi-pronged approach, with the understanding that any one measure by itself is not sufficient to realize a discernible improvement.

As a practicing community pharmacist today, I personally have a greater degree of confidence in the United States drug supply than I did just a few years ago—largely due to the heightened awareness of those in the supply chain to the possibility of counterfeit or diverted medications. That being said, community pharmacists take seriously our role in ensuring the safety of the medications that we personally dispense to our patients and we remain committed to working with our colleagues in the supply chain—other pharmacy organizations, wholesalers and manufacturers—as well as with state and federal authorities to make any needed improvements. Moving forward, it is essential that all stakeholders make a concerted effort to keep the lines of communication open so that consumers can continue to implicitly trust the integrity of the medications that they depend upon.

I appreciate the opportunity to address the Subcommittee today and would be happy to address any questions that you may have. Thank you.

Mr. PITTS. The Chair thanks the gentleman and recognizes Mr. Coukell for 5 minutes for a statement.

STATEMENT OF ALLAN COUKELL

Mr. COUKELL. Chairman Pitts, Ranking Member Pallone, subcommittee members, thank you for the opportunity to present testimony. Thank you for your work on this issue and especially to Representatives Bilbray and Matheson for introducing a bipartisan bill that would help protect Americans from counterfeit and diverted drugs.

My name is Allan Coukell. I am a pharmacist and Director of Medical Programs for the Pew Health Group of the Pew Charitable Trusts.

The safety of the drug supply has been a long-term focus for Pew. Last year we issued a major report, and one of the key findings was that we currently have no national system to detect or prevent counterfeits, and with close to 2,000 individual wholesalers and many more individual pharmacies and actors, it provides multiple points of entry to our system.

Let me illustrate the risks with just a few examples of diversion, theft and counterfeiting. First, the black market for diversion and resale of drugs that have already been dispensed to patients and paid for, often by Medicaid. Two years ago, Federal officials in Florida brought down a ring that illegally purchased $13 million worth of prescription drugs, buying them from patients and then selling them to pharmacies through a licensed wholesaler in Texas. Similar schemes have been documented in other States.

Drug theft is another threat. In 2009, thieves stole a tractor-trailer containing 129,000 vials of insulin. After disappearing for several months, some of this temperature-sensitive drug was later found on the shelves of chain pharmacies in Texas, Georgia and Kentucky. In another case, thieves cut through the roof of an Eli Lilly warehouse in Connecticut using forklifts to load a truck with $75 million worth of prescription drugs. The fate of those drugs isn't known, but some experts believe that the thieves may be letting the alarm die down before selling them back into the system.

And then finally, we have incidents of outright counterfeits. In recent weeks, a counterfeit cancer drug, Avastin, made its way reportedly from Egypt through multiple European countries to a licensed U.S. pharmaceutical wholesaler that had been supplying numerous clinics. In 2001, counterfeit Serostim, a high-cost injectable for AIDS patients, was found in at least seven States and passed through multiple wholesalers. The manufacturer of that drug has since put in place a secure distribution program with a unique serial number assigned to each vial that must be verified by the dispensing pharmacy.

Unlike for that drug, for most drugs there is no currently no way to check whether they are authentic or counterfeit. Some State laws exist. California is implementing a comprehensive system under which manufacturers will put a unique serial number on each unit, and wholesalers and pharmacies will check to ensure that the drugs they buy and sell are authentic.

A strong national standard would be preferable to a patchwork of State laws, but a national system has been under discussion for

years and won't happen without legislation. Congress is now considering a compromise proposal developed between various industry sectors, and Pew supports a number of the elements of this proposal including strengthened standards for wholesaler licensure, but the proposal falls short in a couple of crucial aspects.

First, the key to improved security of drug distribution is knowing who handles the drugs as they move from manufacturer through a succession of wholesalers to the pharmacy or the hospital and ultimately to the patient. The industry proposal calls for tracking drugs at the lot level, but a lot, as we heard already this morning, can contain numerous cases and many thousands of individual bottles and each case or individual unit can be sold separately, and tracking by lot doesn't allow industry or regulators to ever know who bought and sold a given drug.

Maintaining data about lots may provide an incremental benefit over the status quo, but it would fail to catch unsafe drugs in many scenarios. If part of a lot was stolen and illicitly reintroduced into commerce, a pharmacist or a patient would have no way to tell if the product on their shelf was compromised. That same lot will be sitting on the shelves of dozens or hundreds of pharmacies, but if individual units are tracked, specific stolen bottles could be identified.

While the PDSA proposal would result in a unique serial number being placed on each unit of sale, keeping track of the drugs would be impossible unless the serial numbers can be associated with the case in which they are shipped. Even if we decide that we don't need unit-level tracing now, the PDSA system proposed would make it difficult or impossible to track drugs at the unit level in the future.

Next, under the proposed system, neither the pharmacy nor any other party in the system would ever be required to verify the authenticity of drugs. A criminal could sell a vial of counterfeit drug with a fake serial number, and no one would detect it because no one would be required to check it. Pew supports required authentication of drug products by the companies involved in distribution as outlined in H.R. 3026, the Bilbray-Matheson bill.

Let me conclude by noting again that the impending California law creates momentum for a single national standard. Such a standard should product Americans today and provide the flexibility of future refinements.

Thank you, and I welcome your questions.

[The prepared statement of Mr. Coukell follows:]

Testimony before the
House Committee on Energy and Commerce, Subcommittee on Health
United States House of Representatives
March 8, 2012
Allan Coukell, Director, Medical Programs
Pew Health Group, The Pew Charitable Trusts

Through research and critical analysis, the Pew Health Group seeks to improve the health and well-being of all Americans by reducing unnecessary risks to the safety of medical and other consumer products and supporting medical innovation.

Risks to the drug distribution system
One of Pew's key findings is that incidents of counterfeiting and drug diversion in this country – while thankfully far less common here than in other parts of the world – are a matter of serious concern. We currently have no national system to detect or prevent such incidents. A few examples will help to illustrate the nature of the risks. First, the black market for resale of government-subsidized medicines. In 2010, three men were indicted for allegedly illegally purchasing prescription drugs—some directly from patients—and selling them to pharmacies through a licensed wholesaler in Texas. Another threat is drug theft. In 2009, thieves stole a tractor-trailer containing 129,000 vials of insulin. This drug, which needs to be refrigerated, disappeared for a number of months, before being sold back into distribution. Finally, we have incidents of outright counterfeits reaching unsuspecting American patients. Just weeks ago cancer patients in the U.S. were exposed to counterfeit Avastin® – a critical chemotherapy agent used to treat numerous types of the disease.

A national serialization and traceability system to secure distribution
The United States lacks a standard system for companies to keep track of our pharmaceuticals during distribution. Congress is now considering a proposal from the Pharmaceutical Distribution Security Alliance. While we support a number of elements of the PDSA proposal, we are concerned that in at least two crucial respects, the proposal, if implemented in its current form, would neither enable the identification of counterfeit medicines nor provide the building block for a more robust system in the future.

The proposed system does not support unit-level traceability
The industry proposal calls for keeping track of drugs by the lot, but a lot can contain numerous cases of many thousands of individual bottles or packs of vials which may be sold separately. Tracking by lot would fail to catch unsafe drugs in many scenarios. For example, if regulators catch criminals selling diverted vials of expensive injectables, they will not be able to find out what legitimate players bought and sold those vials before they were diverted.

The proposed system would not routinely check for, or identify, counterfeit drugs
A key reason to put serial numbers on prescription drugs is to ensure that pharmacies and others who handle the drugs use the numbers to verify the authenticity of the drugs. Under the PDSA proposal, neither the pharmacy nor other parties in the system are required to verify the products they buy and sell. A criminal could sell a vial of counterfeit drug with a fake serial number, and no one would detect it because no one would be required to check it.

In conclusion, we urge Congress to create a robust national system – one that protects patients today and provides the flexibility to ensure we can build upon it in the future.

Testimony before the
House Committee on Energy and Commerce, Subcommittee on Health
United States House of Representatives
March 8, 2012
Allan Coukell, Director, Medical Programs
Pew Health Group, The Pew Charitable Trusts

Chairman Pitts, Ranking Member Pallone and members of the Health Subcommittee, thank you for the opportunity to present testimony. I thank you for holding this hearing and, in particular, applaud Representatives Bilbray and Matheson for introducing a bipartisan bill that would help protect Americans from counterfeit drugs.

Through research and critical analysis, the Pew Health Group seeks to improve the health and well-being of all Americans by reducing unnecessary risks to the safety of medical and other consumer products and supporting medical innovation.

The focus of my testimony today is the drug distribution system – the risks of counterfeit and stolen drugs, and the pragmatic steps Congress can take to reduce those risks.

In July of 2011, Pew released a report entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs."[1] The report, which underwent extensive external review, was based upon information from regulatory and public documents, peer-reviewed journal articles and interviews with dozens of supply chain experts from numerous perspectives. It was informed by a two-day conference we hosted in March 2011 that included representatives of brand and generic pharmaceutical manufacturers, active drug ingredient makers, major and secondary pharmaceutical wholesalers, chain and independent pharmacies, consumer and health professional organizations, the U.S. Food and Drug Administration (FDA), state regulators and independent supply chain experts.

Risks to the drug distribution system

One of our key findings is that incidents of counterfeiting and drug diversion in this country – while thankfully far less common here than in other parts of the world – are a matter of serious concern. We currently have no national system to detect or prevent such incidents. The U.S. pharmaceutical distribution system is sometimes described as a "closed" system, meaning that it is not legal to import drugs that were not manufactured for the U.S. market. However, the system is not closed in the sense that we have over a thousand individual wholesalers licensed, providing multiple points of entry to the legitimate distribution system.

A few examples will help to illustrate the nature of the risks. First, the black market for resale of government-subsidized medicines. In 2010, three men were indicted for allegedly illegally purchasing prescription drugs—some directly from patients—and selling them to pharmacies through a licensed wholesaler in Texas.[2] Similar illicit purchases – some large scale – are well-documented in multiple states.

Another threat is drug theft. In 2009, thieves stole a tractor-trailer containing 129,000 vials of insulin. This drug, which needs to be refrigerated, disappeared for a number of months, before being sold back into distribution.[3] While most of the stolen drug was never recovered, the FDA has said that some of it was found at retail chain pharmacies in Texas, Georgia and Kentucky, having passed through the hands of licensed wholesalers in at least two other states.[4]

In another case, thieves stole $75 million worth of pharmaceuticals from an Eli Lilly warehouse in Connecticut. It was a sophisticated operation, the largest dollar-value loss from a warehouse in U.S. history.[5] The fate of those stolen prescription drugs is unknown, but one investigator who spoke at the Pew conference and who is an expert in pharmaceutical distribution crime believes that a scheme of drug thieves is to steal the product then hold it, hidden, for a year or two, letting the alarm die down before selling it back in to the system.

Finally, we have incidents of outright counterfeits reaching unsuspecting American patients. It is the unfortunate truth that this hearing occurs just weeks after cancer patients in the U.S. were exposed to counterfeit Avastin® – a critical chemotherapy agent used to treat numerous types of

the disease. In 2001, counterfeit Serostim®, a human growth hormone used to treat AIDS-related wasting, was found in at least seven states and passed through multiple wholesalers.[6,7,8] The manufacturer of Serostim® has since put in place a secured distribution program, with a unique serial number assigned to each vial that must be verified by the dispensing pharmacy.[9]

A national serialization and traceability system to secure distribution

The United States lacks strong uniform national standards for licensure of pharmaceutical wholesalers, and we lack a standard system for companies to keep track of our pharmaceuticals during distribution. There is currently no way to check whether an individual vial or bottle is authentic or counterfeit.

Some state laws exist. California has put in statute a comprehensive system that would require manufacturers to put a serial number on each bottle or vial, and would require wholesalers and pharmacies to check the drugs they buy and sell to ensure they are authentic. California's law is scheduled to come into effect three years from now. Despite the strength of the law, a patchwork of state requirements is not ideal either for companies or for consumers.

Manufacturers, wholesalers and pharmacies, as well as the FDA, Congress, and other stakeholders have for years been discussing a federal system to better ensure distribution safety and security as well as facilitate compliance.

Congress is now considering a proposal from the Pharmaceutical Distribution Security Alliance – a consortium that includes many, but not all of the major industry stakeholders. We applaud their efforts to bridge widely divergent views on how best to create a single national standard. We believe that the perfect cannot be the enemy of the good. However, while we support a number of elements of the PDSA proposal (including the interim provisions to increase safety, as well as strengthening federal wholesaler licensure guidelines), we are concerned that in at least two crucial respects, the proposal, if implemented in its current form, would neither enable the identification of counterfeit medicines nor provide the building block for a more robust system in the future.

The proposed system does not support unit-level traceability

The key to improved security of drug distribution is knowing who handles the drugs as they move from manufacturer, through a succession of wholesalers, to the pharmacy or hospital and, ultimately, the patient.

The industry proposal calls for keeping track of drugs by the lot, but a lot can contain numerous cases of many thousands of individual bottles or packs of vials. Each case or vial may be sold separately, and tracking by lot does not allow industry or regulators to ever know who bought and sold a given drug through distribution.

Maintaining data about lots *may* provide an *incremental* benefit over the status quo, but it would fail to catch unsafe drugs in many scenarios.

For example, if regulators catch criminals selling diverted vials of expensive injectables, they will not be able to find out what legitimate players bought and sold those vials before they were diverted. They will only know the lot number – and this lot of drugs could have traveled through multiple distributors and reached multiple pharmacies.

Also, if part of a lot is stolen and illicitly reintroduced into commerce, a pharmacist or patient will have no way to tell if the product on their shelf is compromised. However if unit-level data is kept, specific stolen unit serials could be identified.

While the PDSA proposal would result in a unique serial number being affixed to each individual unit, keeping track of the drugs would be impossible unless the unit serial numbers can be associated with the case they are shipped in. The PDSA proposal explicitly excludes this so-called "aggregation" of serial numbers. If a system is constructed as proposed, it will be difficult or impossible to track drugs at a more granular level in the future.

The proposed system would not routinely check for, or identify, counterfeit drugs

A key reason to put serial numbers on prescription drugs is to ensure that pharmacies and others who handle the drugs use the numbers to verify the authenticity of the drugs. Under the PDSA

proposal, neither the pharmacy nor other parties in the system are required to verify the products they buy and sell. A criminal could sell a vial of counterfeit drug with a fake serial number, and no one would detect it because no one would be required to check it.

Pew supports required authentication of drug products by companies involved in distribution. Required checking would help ensure fake or otherwise flagged serials are caught, and not allowed to make it to patients. Such a requirement could have kept the unsafe insulin, sold back into distribution after it was stolen, away from the patients who instead experienced poor blood sugar control. Such a requirement would also support enforcement of responsible purchasing by wholesalers and pharmacies

Conclusion

The risk of stolen or counterfeit products reaching and harming patients through the drug distribution system is small, but real. Recently, both the U.S. Counterfeit Pharmaceutical Inter-agency Working Group and the office of the U.S. Intellectual Property Enforcement Coordinator have recommended implementation of a track-and-trace system to secure drug distribution against counterfeits in separate March 2011 reports.[10,11] The impending implementation of California's law creates momentum for a single national standard. In 2008, major industry stakeholders committed to being ready for the California law by 2011. Similar promises were made when the law's implementation was delayed until 2015. We urge Congress to create a robust national system – one that protects patients today and provides the flexibility to ensure we can build upon it in the future.

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[11] Administration's White Paper on Intellectual Property Enforcement Legislative Recommendations. March 2011. http://www.whitehouse.gov/sites/default/files/ip_white_paper.pdf. Accessed April 22, 2011.

Mr. PITTS. The Chair thanks the gentleman and thanks all the witnesses, and we will begin questioning. I will recognize myself for 5 minutes for that purpose.

Let me ask a question to all of you first. You can each respond. We are all concerned about the safety of our drug supply, and we want to ensure that diverted drugs and counterfeit drugs do not reach our Nation's patients. However, as we look at policies to help, we also have to think about the cost to our Nation's small businesses. They are struggling right now. We need to take them into account as we analyze every policy idea.

The first question, how do we ensure the safety of our prescription drugs in the most cost-effective way? And then two, why is a national standard necessary? Mr. Brown?

Mr. BROWN. I think I would say the PDSA model, we have got a consensus throughout industry from chain drugstores, independent pharmacies, secondary wholesalers, third-party logistics providers, brand and generic manufacturers. We believe this is a scaleable system and a feasible system that we are proposing, and I think that this will help to achieve all of FDA's stated goals, one of which being to prevent introduction and to help identification of counterfeit medicines. We are concerned about the cost as well, but the system that we are proposing is exponentially less than the system would be if we had to implement the California model, which we don't think is technically feasible.

Mr. PITTS. Ms. Gallenagh?

Ms. GALLENAGH. I would agree with Mr. Brown. We believe that the best approach is something that is done at the national level, and our members have told us that it would be more cost-effective to operate the RxTEC proposal that PDSA has put forth and that we have worked on rather than work toward California and then deal with potentially New York or Illinois or whatever State is next in this arena. We are already—as wholesalers, we see firsthand the 50–State patchwork that you hear so much about, and that really is a reality for our members in terms of dealing with 50 different laws, and so automatically we think that we get greater efficiencies and cost benefits from going with the PDSA proposal.

Mr. PITTS. Dr. Davis?

Mr. DAVIS. The PDSA proposal also looks at the problem in a multifaceted approach. The only place that rogue pharmacies can get counterfeit or diverted medications is from rogue wholesalers, so we need to look upstream. I think the PDSA looks at creating national standards to help us feel that the drug supply above us is intact. I also feel that it takes a look at the rules and regulations set against counterfeiters to prevent that sort of activity long before it gets to a pharmacy level, and I think that the infrastructure built on the serialization and lot numbers included in the RxTEC Act prepare this for adaptation in the future. We need a system that is going to adapt to the health care needs of the near future, not necessarily the legislative needs that we foresee coming, and this market is going to continue to change and the products that we are going to experience are going to continue to change, positioning us very well to scale effectively.

Mr. PITTS. Mr. Coukell?

Mr. COUKELL. Mr. Chairman, along with the compliance, or the costs of compliance that my colleagues raise, I think the other argument for a national system is that the companies involved in drug distribution work across State lines, so in the case of Avastin, it was a Tennessee-licensed wholesaler that sold the drugs but they ended up in Illinois, Texas and California, or at least those are the practices that have been mentioned. So that argues for a national standard, and clearly we have to do it in a way that has the least necessary cost impacts. So it is important to say what are the goals of the system, do we want to be able to identify counterfeit drugs when they come in, and if so, what is the most effective way to do that, and secondly, do we want to be able to track product as it moves through the system and what is the most cost-effective way to track the product at the level we want to be tracking it at.

One of our concerns with the proposal is that companies are going to make a capital investment to be able to serialize their product, and we certainly recognize they are stepping forward to do that, and I think the question we have to ask is, if we think that eventually we want to get to a system where we are tracking individual units and we are putting into place an infrastructure now that is lot-level tracking, are we going to be back here in 5 or 8 years when we have a crisis because have counterfeit drugs on the shelves asking them to invest again in a new system to track at the unit level or should we get it right now.

Mr. PITTS. Mr. Brown, can you speak what would the costs be to manufacturers if the California approach were adopted?

Mr. BROWN. Yes, I can give you an approximate estimate. If we think about the number of packaging lines that serve the consumers in the United States, it is about 3,000. I have heard some estimates higher, some lower, and per packaging line, my manufacturers tell me that it ranges between $500,000 and $1 million per packaging line. So at the highest, I would say it is near $3 billion just to implement the camera infrastructure. We are not talking about the data management costs or the costs of the barcodes, the ongoing costs. We are just talking about getting the infrastructure set up into the packaging lines.

Mr. PITTS. My time is expired. The Chair recognizes the ranking member for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I was going to ask actually each of the panelists this question. In addition to the various provisions related to development of the RxTEC system, the proposal from the Pharmaceutical Distribution Security Alliance contains a number of provisions related to Federal licensing of parties involved in the manufacture and distribution of pharmaceuticals. I understand these provisions are intended to create Federal uniform for the regulation of these parties and could help prevent bad actors from engaging in the drug supply chain. But I would like to ask each of you if you support the provisions requiring Federal licensure for manufacturers, distributors, repackagers and third-party logistics providers, and if not, what concerns they have. And I am just looking for a yes or no at this point.

Mr. BROWN. Yes.

Mr. PALLONE. Ms. Gallenagh?

Ms. GALLENAGH. We support the provisions that are contained in the proposal, but if I could clarify, on the wholesaler licensure piece, we support Federal standards and still retain the issuances of licenses with the State.

Mr. PALLONE. OK.

Mr. PALLONE. Dr. Davis, do you agree with that?

Mr. DAVIS. We agree as well.

Mr. PALLONE. Mr. Coukell?

Mr. COUKELL. As do we.

Mr. PALLONE. Now, let me ask Mr. Coukell, I understand that from the patient safety perspective, the best system would be one in which the pedigree system goes to the unit level—you talk about this—in which the pharmacist verifies the pedigree of all the units he receives for dispensing. I also understand that the current industry proposal does not have serialization information down at the unit level but it enables tracing back only to the lot level. You stated that, or one of you did. Meanwhile, that proposal does not require a pharmacist to verify any pedigree information whatsoever before dispensing, although it would facilitate traceback once the problem has been identified. So it appears that the industry proposal does not go as far as some would like and certainly not as far as the California law appears to go. However, what many of us have heard is that the California law is proving much more difficult to implement than anticipated and that the industry plan can serve as a building block towards reaching the goal that California law sets out.

So my question, I will ask you first, Mr. Coukell, is, do you agree with that, what I just said, or do you see the industry proposal as a step that while containing many useful items ultimately puts a roadblock in front of ever reaching unit-level tracing and verification, and I will ask Ms. Gallenagh if you would respond as well?

Mr. COUKELL. Thank you for that question. If I could begin with one point of clarification, under the industry proposal, there would be a unique serial number on each vial. It just wouldn't be tracked as it moved through the system. So potentially, on a case-by-case basis, somebody could look that up and check it. But what you don't have is at the point where there is no suspicion that vial being checked and, you know, these counterfeits are pretty good. You can't by the naked eye in a lot of cases detect them and so there is no system here where a flag is automatically thrown up.

So I think the key question in looking at how to move forward is, what are the basic elements that we want now and what are the basic elements that we are going to want within a reasonable time frame, and does this system give us enough to build on, and as I said already, we are a little concerned that if we go with this system, then we may not be able to get where we need to go in the future.

Mr. PALLONE. OK. Ms. Gallenagh?

Ms. GALLENAGH. Sure. Thank you, Congressman. I think a couple of things in this area. One, I am to agree with Mr. Coukell's explanation. There is an SNI or serial number included in the RxTEC data, so the 2D barcode would include the SNI information as well as lot and expiration. What we think is that that would

alone for the first time provide unique identification of medicines and would be a very big step for the industry. Today we don't have that at all, and we are dealing with paper and electronics sometimes, always lot level and no real standard in terms of what different States are doing across the country. I think we also would think that going with the PDSA proposal is not a roadblock but sticking with the 50–State patchwork may be a roadblock to actually ever getting to a true electronic system across the country. I think that, you know, we need to take a broader perspective of this issue and that patient safety really does belong in the purview of Congress right now. Right now is probably the best opportunity we have, and we do have industry consensus and that is something that we have never achieved before, and so I think that goes a long way, and I believe that my members, other industry partners, once those things are in place that are put forth in the PDSA proposal like unit-level serialization, I think that building on the innovation that we have built on in the past and the efficiencies that can be achieved as we learn more about the technology, we may eventually find other uses for the technology and it may go further than what we have initially set out to do.

Mr. PALLONE. Thank you.

Thank you, Mr. Chairman.

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

Mr. BURGESS. Thank you, Mr. Chairman.

Dr. Davis, you were probably in the room earlier when Dr. Woodcock was here and you heard our exchange about the drug shortages. She had been here 3 or 4 weeks ago, and this was a lot of follow-up to that. Can you tell me from a community pharmacist's perspective what you are encountering in the drug shortage arena?

Mr. DAVIS. A single day doesn't go by where drug shortages don't affect patients in one manner or another. So of the hundreds of prescriptions that we fill daily in my pharmacies, we know we have to have a conversation every single day with a patient to alter therapy, to choose a different therapy or to come to a consensus with the prescribers and other caregivers as to how to change therapy to still get the best result for that patient without the agent available that we need.

Mr. BURGESS. Can you give us some examples of how that might come up in the course of your day? What are the ones you are seeing very frequently? You heard my exchange with Dr. Woodcock. We had the executive order in October, and as far as I can tell, not a darn thing happened. But then when we had a very intense discussion about Doxil 3 or 4 weeks ago, suddenly you got some movement on that and people were able to find oh, yes, there is some supply that we could free up. So help me here. Tell me what you are having the most trouble with. I will write a letter to Dr. Woodcock. We will see what we can do.

Mr. DAVIS. The most trouble that is arising is mostly solid dosage forms. At the community pharmacy level, we dispense very few injectable medications or infusible medications so the cancer drugs that you are referencing are not necessarily a problem in the com-

munity, but what we do see are the ADHD medications, solid dosage forms of those, medications in some neurological disorders as well. Methotrexate has been recently a problem for us in the treatment of RA and a couple of other disease states. And in those cases, they are patients that were managed and well managed on these medications and now we have disruption of therapy. So we have to make a decision, can we still achieve the clinical outcomes with another agent, and it is proving to be burdensome. It is proving to burn time that we shouldn't necessarily have to burn because this patient has already been managed effectively and efficiently within the system.

Mr. BURGESS. How involved do you get with cost of prescriptions? I get to do a number of telephone town halls with other Members of Congress because they like for me to be there, and invariably a caller calls and they are on whatever and it is frightfully expensive, and then you kind of know in the back of your mind, there is a generic available for that that probably is much less. How do you handle that at the community pharmacy level when somebody is having difficulty paying for their medication and there might be a generic or there might be something that is just a little bit different but perhaps suitable? Do you communicate with the physician, the prescribing physician, in those instances?

Mr. DAVIS. Absolutely. Something to keep in mind is, we are probably the only health care professional that actually gets to see the cost of care as it is rendered, so as someone is standing in front of us approaching the instance of therapy, we know what that is going to cost and how that is going to impact that patient. We are also the only professional that still has one-on-one time to render to those patients to help them understand and navigate the waters associated with the cost of those medications. So we do reach out to our prescribers in the community and offer recommendations based on what we understand to be the outcomes and efficacy of that drug while still maintaining the integrity of the intent of that prescriber but being able to do it at a lower cost.

Pharmacists are doing it each and every day over and over again throughout their day. It is not necessarily a recognized function but we have transitioned from being the makers of salves and potions into clinically based social workers and helping people to navigate Medicare, helping people to navigate Medicaid, helping people to understand what is going on with the PBMs and the cost of their medications.

Mr. BURGESS. Let me ask you this because the issue of Avastin came up, and I have to admit, a couple weeks ago I was pretty taken by surprise. Now, I get why Viagra might be a counterfeit and why there might be a market, you know, the incredible markup that occurs on that, but Avastin is hardly something you would just buy on the Internet and use. What is going on there?

Mr. DAVIS. So the concern that I have is, it is a high-dollar medication so clearly to be able to counterfeit and move that into the supply chain puts a lot of value not only on the people that are actually counterfeiting and entering it in the supply chain but the hands that may touch it during the supply chain itself. And that is why I said, the integrity of our trading partners is of utmost importance, especially being the end dispenser of that. So to under-

stand the components of the supply chain that come before us, to understand who your wholesaler is, to understand the integrity associated with that wholesaler and how they conduct business is vital to what we do at the community and ground level.

With the case of Avastin, I understand that that particular medication changed hands through multiple sources multiple times after entering this country and did not necessarily enter through the channels that we would normally consider as part of the trusted lines.

Mr. BURGESS. It wasn't in the legitimate stream of pharmaceutical commerce?

Mr. DAVIS. Correct.

Mr. BURGESS. Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

That concludes our third and final panel. It has been very informative. We thank all of you for your testimony.

I will remind the members that they have 10 business days to submit questions for the record, and I would like to ask the Director and witnesses to respond to the questions promptly. Members should submit their questions by the close of business on Thursday, March 22nd.

Without objection, the subcommittee is adjourned.

[Whereupon, at 2:35 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED TWELFTH CONGRESS

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House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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WASHINGTON, DC 20515–6115

Majority (202) 225–2927
Minority (202) 225–3641

April 4, 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 "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain" on March 8, 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 carly.mcwilliams@mail.house.gov by the close of business on Tuesday, April 17, 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

JUL 10 2012

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the March 8, 2012, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain." This letter provides responses for the record to questions posed by certain Members of the Committee, which we received on April 4, 2012.

If you have further questions, please let us know.

Sincerely,

Jeanne Ireland
Assistant Commissioner
for Legislation

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. **There are concerns regarding the lack of obesity medications and clear guidance for sponsors pursuing new treatments against this significant public health problem. Please update the Committee on the Agency's efforts on this issue, including the status of any reports requested by Congress.**

Obesity is a significant public health concern and FDA is committed to working with sponsors to approve safe and effective drugs to treat obesity. As you may be aware, FDA has removed multiple drugs from the market over the past 20 years due to risks of serious cardiovascular adverse events, including stroke and damage to valves in the heart. Another drug for obesity that was approved by the European Medicines Agency in 2006, but not FDA, was later withdrawn from the European market in 2008 due to an increased risk of suicide.

We are pleased to report that on June 27, 2012, FDA approved Belviq (lorcaserin hydrochloride) as an addition to a reduced-calorie diet and exercise, for chronic weight management. The drug is approved for use in adults with a body mass index (BMI) of 30 or greater (obese), or adults with a BMI of 27 or greater (overweight) and who have at least one weight-related condition such as high blood pressure (hypertension), type 2 diabetes, or high cholesterol (dyslipidemia). Belviq is manufactured by Arena Pharmaceuticals GmbH of Zofingen, Switzerland, and distributed by Eisai Inc. of Woodcliff Lake, N.J.

FDA is working with stakeholders, such as patient and physician groups, to explore the complex issues related to development and approval of drugs to treat obesity. These interactions include an FDA public advisory committee meeting that was held March 28 and 29, 2012, and participation in a series of roundtable meetings spearheaded by George Washington University (GWU) that includes key players in the obesity community. FDA is participating in the GWU-led discussions as observers, and we will be participating in several roundtable meetings in 2012. These meetings provide a forum to discuss clinical trial designs, endpoints, and indications for drugs to treat obesity. Both the public advisory committee meeting and the GWU effort are important steps for FDA as we continue the process of developing guidance for obesity drugs.

Regarding reports requested by Congress, FDA's Report to Congress on Obesity Therapeutics was delivered on January 30, 2012, in response to the Senate Report 112-073 that accompanied the FY 2012 Agriculture, Rural Development, Food and Drug Administration and Related Agencies Appropriation Bill.

2. **As part of the 2012 User Fee Authorization, the Committee is considering adding new incentives for manufacturers to develop new antibiotics to treat resistant infections. Section 4 of Public Law 110-379 included a provision to provide equitable treatment under Hatch-Waxman for so-called "old" antibiotics approved prior to 1997. Would you please provide an update on the implementation of this law, including (a) how many applications the FDA has received to date for old antibiotics under the 2008 law,**

(b) the result of those applications, (c) the average timeline for consideration of these applications, and (d) any issues the FDA has encountered on implementing the law.

a. **How many applications has FDA received to-date for old antibiotics under the 2008 law?**

FDA received only one new drug application (NDA) for approval of an "old" antibiotic for which the applicant requested three-year Hatch-Waxman exclusivity under the 2008 law. FDA also received a supplemental NDA and related three-year exclusivity request from ViroPharma, Inc., the sponsor of already-approved Vancocin (an "old antibiotic"), seeking changes to the approved labeling.

b. **The result of those applications.**

FDA approved the NDA for Sklice (ivermectin) on February 7, 2012, and it received three-year, new-product exclusivity. FDA approved ViroPharma's supplemental NDA and denied ViroPharma's exclusivity request for vancomycin on December 13, 2011. The company sued FDA on April 13, 2012. On April 23, 2012, a District of Columbia district court denied ViroPharma's motion for injunctive relief on this issue, concluding that FDA's interpretation of the relevant provision limiting availability of the exclusivity for old antibiotics was reasonable. That lawsuit is still pending.

c. **The average timeline for consideration of these applications.**

As noted above, FDA received only one NDA under the 2008 law. FDA approved the application (for Sklice), after a 10-month review, on February 7, 2012. FDA approved ViroPharma's supplement NDA and denied the company's exclusivity request, after a six-month review, on December 13, 2011.

d. **Any issues the FDA has encountered in implementing the law.**

FDA has not encountered issues implementing this law.

<u>The Honorable Phil Gingrey</u>

1. **One area in which I am particularly concerned are broad spectrum antimicrobial products that would provide both biodefense as well as commercial application. I know BARDA, in addition to NIAID and DTRA, are supporting efforts to develop products against serious national security threats like plague or tularemia.**

   a. **How could we better incent biodefense-focused manufacturers to consider entering R&D programs for commercial applications, as well as incent commercial manufacturers to consider applying their work to our countermeasure needs?**

Robust incentives for antibacterial drug development could have an important role in stimulating antibacterial drug development to address public health needs. Stimulating antibacterial drug development for both commercial use and biodefense use could provide value in both areas. Many of the countermeasures that we plan to rely on for biodefense are drugs that were primarily developed for commercial use. Incentives that support research and development (e.g., "push" incentives, such as grants to support development of new products) and awards for successful development of a new product (i.e., "pull" incentives) could both contribute to stimulating antibacterial drug development. The precise mix and level of incentives to achieve an appropriate level of stimulation is a difficult question. However, there is a need for the development of new antibacterial drugs to treat patients' infections. Given the biology of antimicrobial resistance, this need will continue. Ideally, with development of new antibacterial drugs and prudent use of antibacterial drugs, we will be positioned to have new therapies that we can rely on for the treatment of patients' infections. In addition to various incentives, establishment of infrastructure and methodologies to conduct trials could help to facilitate the testing and development of broad spectrum antimicrobials.

b. **Would Priority Review Vouchers or another type of incentive be helpful in that regard?**

FDA is concerned about the potential adverse public health impact of granting Priority Reviews to applications that would normally not merit a priority designation. Our Priority Review policy is designed to expedite the review of applications for drugs that will bring improvement to existing treatment options. If applications that would not normally qualify for Priority Review are required by law to receive a Priority Review, there is likely to be an adverse impact on FDA's ability to review and act on true priority applications in a timely manner, which would delay the approval of important new drugs. In effect, given FDA's limited resources, if more applications are a priority, then the value and FDA's ability to actually complete its review of priority applications in six months will be diminished. It would be preferable to consider other types of incentives, such as the incentives noted previously, as a means to stimulate antibacterial drug development.

2. **We feel the GAIN Act provides a proper and manageable jumpstart to the antimicrobial arena. We know there is certainly more that can be done, as it's imperative that we spur new product development. Can additional concepts such as providing greater market exclusivities for certain novel products, better valuing antibacterials that are "game-changers", or less rigorous requirements for approval at FDA spur further antibiotic development?**

Conceptually, it seems that there are at least two important prongs that could support the field of antibacterial drug development. First, there is an immediate and critical public health need to

develop new antibacterial drugs for treating patients with serious or life-threatening bacterial infections, who currently lack satisfactory treatment options (i.e., areas of unmet need). Second, there also is considerable public health value in stimulating or "jumpstarting" antibacterial drug development more generally. Given the time that it takes to develop a new antibacterial drug from discovery through to market availability, there is value in having a robust pipeline of new antibacterial drugs that can be used to provide new options to treat patients with infections of today and also patients' infections with bacteria that we can expect will arise in the future that don't respond to available therapies (e.g., bacteria resistant to existing therapies or newly emerging pathogens). In addition, it is important to note that the development of new antibacterial drugs that are better tolerated by patients, that have fewer adverse effects, or that avoid certain drug interactions also have public health value.

The Honorable Bill Cassidy

1. To follow up on my questioning at the hearing, I am very concerned with recent reports on counterfeit drugs entering the supply chain through online pharmacies. I know that you share my concern as you mentioned that more work needs to be done in this area. The National Association of Boards of Pharmacy cites that 96% of sites are not in compliance with State and Federal law. Does the FDA have staff designated to the protection of patients from these dangerous sites? I am curious if the FDA has a budget allocated for any consumer educational activities surrounding internet pharmacies. If not, is this something that will be included in future budgets?

FDA shares your concerns to protect U.S. consumers and the drug supply from potentially harmful products. Because many online pharmacies are located outside the United States; because of the ease of moving, redirecting, and re-establishing websites during and after enforcement actions; and because of the sheer volume of Internet sellers advertising the sale of various drugs, it is challenging for FDA to combat illegal online pharmacies and the individuals selling these products. FDA has designated staff and resources to tackle supply chain issues and public education related to online pharmacies, which includes staff in a newly created Office of Drug Security, Integrity and Recalls within FDA's Center for Drug Evaluation and Research, Office of Compliance, and staff in the Office of Regulatory Affairs' (ORA) Office of Criminal Investigations (OCI) and Office of Enforcement (OE).

Educating U.S. consumers is the primary tool FDA uses to increase the public's awareness about buying drugs online safely and about the dangers and risks associated with purchasing prescription drugs from illegal online pharmacies. FDA designated a one-time allocation of funds in FY2010 to improve our "How to buy medicines online safely" campaign and to develop educational tools for consumers. FDA recently launched a health fraud website at *www.fda.gov/healthfraud*. We are also trying to better understand consumer and health care professional perceptions, including perceived safety risks, about the online purchase of prescription drugs as we embark on our public education campaign to inform consumers about illegal online pharmacies. FDA plans to collaborate with both governmental and non-governmental partners to disseminate educational information to raise awareness.

To more effectively use our current resources, FDA continues to enhance its relationships with foreign law enforcement and regulatory authorities and other international partners to work together to curb online sales and distribution of counterfeit and illegal medical products.

The Honorable Edolphus Towns

1. The challenge of implementing PDUFA IV is well documented, with the first two years of FDA performance being pretty poor in meeting review times. Much of that is not FDA's fault. You had to hire and train a number of new reviewers and figure out how to apply new authorities like REMS. PDUFA V has a good deal for FDA with more money and longer review times, but the agreement has significant changes to the review process. What is FDA doing to train reviewers in the new process and get ready for October 1 so we don't see a repeat of the first two years of PDUFA IV?

Programs, initiatives, and implementation plans are currently in development to train staff and address the proposed PDUFA V commitments. An organizational workgroup of review staff has already completed the updates of the review management process document, and discussions are underway to identify training needs to communicate these changes to relevant staff. At the same time that PDUFA IV was enacted, FDA was required to implement many new authorities within certain time frames. Addressing these new requirements had a small and temporary adverse impact on FDA's ability to meet the application review performance goals. FDA quickly recovered since that time and has either met or exceeded nearly all review performance goals for the last two fiscal years.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED TWELFTH CONGRESS

Congress of the United States
House of Representatives
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Majority (202) 225–2927
Minority (202) 225–3641

April 11, 2012

Mr. Shawn Brown
Vice President
State Government Affairs
General Pharmaceutical Association
777 6th Street, N.W., Suite 510
Washington, D.C. 20001

Dear Mr. Brown:

Thank you for appearing before the Subcommittee on Health on March 8, 2012, to testify at the hearing entitled "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain."

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 then (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions by the close of business on Tuesday, April 25, 2012. Your responses should be e-mailed to the Legislative Clerk, in Word or PDF format, at Carly.McWilliams@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: Mr. Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

April 25, 2012

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
420 Cannon House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health
237 Cannon House Office Building
Washington, DC 20515

Dear Chairman Pitts and Ranking Member Pallone,

GPhA would like to submit the following in response to your recent additional questions for the record for the March 8, 2012, hearing before the Subcommittee on Health entitled "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and downstream Pharmaceutical Supply Chain."

The Honorable John D. Dingell

1. **The Proposal put forth by PDSA would phase in requirements for manufacturers, repackagers, wholesale distributors and dispensers, with the RxTEC system to be fully operational 6 years after regulations have been promulgated. Is the time table laid out in RxTEC achievable?**

   Yes. GPhA, along with other supply chain stakeholders involved in the Pharmaceutical Distribution Security Alliance (PDSA) believe the proposal is technologically feasible, scalable to a national level, and achievable within the proposed time frame. From a manufacturer perspective, we believe 3 years from final regulations to implementation is a minimum under RxTEC due to the equipment installation and testing that will be required for compliance. Other systems might take more or less time to implement.

2. **In your testimony you comment on the cost of implementing a full track-and-trace system. Can you please provide an estimated cost to a manufacturer to implement a full track-and-trace system?**

   While all sectors will make significant investments even under the proposed RxTEC model, entities across the pharmaceutical distribution chain believe that compliance with a federal RxTEC model would cost less and reduce the regulatory burdens when compared to compliance with a system like the one envisioned by California. GPhA strongly believes RxTEC will enhance patient safety and supply chain security. Moreover, a federal system will enable industry participants and regulators to harmonize operations on a global basis, yielding significant cost savings and investment efficiencies while enhancing safety and security worldwide.

   Pharmacies
   A June 2008 Accenture report commissioned by the National Community Pharmacists Association (NCPA) and the National Association of Chain Drug Stores (NACDS) estimated it could cost from $84,000 - $112,000 per store to implement a nationwide track & trace system,

similar to what is required by the CA law, plus additional costs to maintain and operate the system in subsequent years.

Implementation costs for such a system would vary among large, medium, and small chain pharmacies, as well as independent pharmacies:

	Per Pharmacy Data Center Costs	Per Distribution Facility Costs	Per Pharmacy Store Costs
Large	$6,133,305	$2,881,181	$112,129
Medium	$2,288,265	$2,752,771	$103,939
Small	$99,900	-	$90,399
Independent	$33,300	-	$84,102

Accenture Report (June 2008)

Pharmacies anticipate lower costs to comply with a nation-wide RxTEC model than to comply with CA or other similar pedigree or track & trace type systems.

Wholesale Distributors
Some small wholesale distributors estimate facing 10 times higher costs to comply with CA than under the RxTEC model.

Some large wholesale distributors estimate facing 5 – 8 times higher costs to comply with CA than under the RxTEC model.

Generic and Brand Manufacturers
Some brand and generic manufacturers estimate 2 -5 times higher costs to comply with CA than under the RxTEC model.

Manufacturers estimate it could cost $500,000 to $1 million to retool one packaging line. Currently, approximately 3,600 packaging lines supply the US pharmaceutical market, meaning it could cost $2 – $3.5 billion to add the serialization plus aggregation functions necessary for compliance with CA's pedigree law. In addition, GPhA estimates about 20% annual operating expenses per line (i.e., if line costs $1M, annual operating expenses would be $200K), which does not include extra returns, line stoppages, etc. Further costs that are not calculated in the estimates below include databases, pedigree systems, and alterations to warehouse management systems, ERP systems and workflow/process changes.

Estimates from some manufacturers:

Packaging Line	Estimated Packaging Line Costs with Aggregation (like CA)	Estimated Packaging Line Costs without Aggregation (under RxTEC)	Estimated Difference in Costs
Blister line	$750,000	$200,000	$550,000
Bottle line	$550,000 to $1 million	$150,000 to $260,000	$290,000 to $850,000
Manual line	$500,000	$200,000	$300,000

All sectors
The systems and infrastructure that sector stakeholders will need to build in order to manage and maintain the data required under a pedigree system like the CA law is estimated to cost sector stakeholders more than $100 million each, which would significantly increase if stakeholders had to comply with a patchwork of state and international requirements.
The exponentially higher costs and unproven system requirements of other pharmaceutical distribution chain security models could lead to interruptions in pharmaceutical product distribution, and have a significant impact on access to and costs of healthcare for governments and patients.

Under burdensome state requirements, some companies may restrict operations, e.g., only distribute medical devices or other products exempt from the pedigree requirements, and some may be forced to go out of business, including pharmacies and wholesalers. Numerous manufacturers anticipate that their business in California is not large enough to justify the cost of compliance—meaning that companies would potentially choose to not sell products into California.

For example, for one small wholesale distributor who has one location and annual sales of about $25 million, the costs of complying with a pedigree system like CA would wipe out more than 100% of such company's income after expenses in just one year.

According to Accenture, the estimated per pharmacy costs to comply with a nationwide track & trace system similar to the CA law would consume nearly 2% of a retail pharmacy's total annual pharmacy sales, which is significant in an industry which averages an annual net profit of about 3%. Because pharmacy is a low margin business, any increase in costs put great pressure on a pharmacy's ability to continue to operate.

Stakeholders across the pharmaceutical distribution chain believe that moving towards a federal RxTEC model will help mitigate the negative economic consequences that are expected to result from the high costs and burdens of implementing burdensome state requirements like the CA pedigree system.

3. **Will the RxTEC system be more affordable to manufacturers?**
Yes. As noted above, the costs of a system, such as the one taking effect in California in 2015, that includes aggregation of unit level data with case level data, are exponentially greater than the system proposed by the PDSA.

4. **You also state in your testimony your belief that the California model would be prone to error. Can you please explain why you believe that to be the case?**
The California model would require the recording of each change in ownership of the smallest saleable unit of medicine, so that the entire distribution history of an individual unit could be tracked and traced by scanning a unique serial number affixed to each product. No technology or database exists today that could reliably support management of tracking and tracing unit level data throughout the entire supply chain. For instance, Radio Frequency Identification (RFID) technology, which had at one time been considered for use as a serialization technology for pharmaceuticals, is significantly flawed because the readability of the RFID tags is not reliable; for example, the readability of RFID is negatively affected by liquid dosage forms, foil packaging, and the positioning of the tag within the package or case. Thus, the certification aspects of California's law will be difficult, if not impossible to comply with due to the inaccuracies of vision systems and other technologies integral to this process. Since failure of certification could mean criminal penalties, the supply chain will become slower and more conservative, again, potentially aggravating shortages and slowing production. There are approximately four billion prescriptions dispensed to patients in the US per year; products reach consumers through many more billions of transactions throughout the supply chain. Any misread or error in recording such data would require the manufacturer or owner of the product to stop production or shipment in order to resolve the error. On a commercial scale where stakeholders would be required to record data on billions of units distributed through billions of transactions, even a small error rate would slow distribution to a crawl, leading to large scale product returns, potential creation or worsening of drug shortages and higher consumer prices due to the cost and complexity of the system.

5. **Can you please explain how the RxTEC system will minimize the potential for error?**
Generic and brand manufacturers have committed to serializing individual units of medicine using 2D barcodes, a reliable and well established technology. Using 2D barcodes reduces or avoids issues with read rate failures associated with RFID that can result in undue delays or returns of shipments, which increase costs and may contribute to drug shortages and higher prices for the consumer. For instance, modern scanning equipment is capable of error correction in instances where a barcode may be smudged, scratched or obscured. 2D barcode scanners are capable of reading curved surfaces, thick printing, faded or overlapping print, and low contrast or in uneven lighting.
Manufacturers are also committing to maintaining a database that would allow regulatory authorities or other stakeholders to verify the legitimacy of those serial numbers commissioned for a particular lot. The RxTEC model would create an association between unit level data and the lot number. Wholesalers would be able to capture this data. Today, wholesalers do not record the lot data, but using the RxTEC code, wholesalers will be able to track particular lots of product sold to particular customers. Pharmacy, unlike today, will easily be able to determine with certainty which specific lots they have received and where the products came from. The lot data associated with shipments is collected by scanning the RxTEC code during the "picking" process for outbound shipments from a wholesaler. Using the RxTEC code, wholesalers also intend to record date-of-receipt of particular lots of inbound product. Lot control is an enormous advancement over current practices and wholesalers have agreed to various means of using the

serial number portion of the RxTEC code within their internal processes. These capabilities would help to ensure fewer errors in the distribution system at large, and close potential loopholes in the distribution system that may be vulnerable to the intrusion of counterfeits today.

6. **As you know manufacturers will be required to have systems in place to support lot level tracing and maintain records that associate serial numbers to product and lots. How will lot level traceability help manufacturers identify where in the distribution system a diversion or contamination occurred?**
First of all, the RxTEC system outlines stricter licensing requirements for wholesalers and more sharing of data between supply chain trading partners. In general, this would make infiltration of the legitimate supply chain more difficult for criminals.

If a diversion or contamination occurred for a specific lot of a prescription product, using the RxTEC system, one could quickly determine who had handled (or claimed to handle) that lot. Manufacturers will maintain records (purchases, receipts, invoices) of which customers received a specific lot and quantity. Distributors will also maintain records of which of their customers received a specific lot, and the quantity received. This system will allow stakeholders or regulators to determine those entities that had possession of products from a specific lot from any point in the supply chain upstream and to see the pathways that specific lot numbers took to reach retailers. The universe of stakeholders and of potential rogue players will be narrowed down very quickly and a focused investigation of upstream/downstream/lateral exchange of product/lot/quantity ownership information can be undertaken, revealing gaps in offsetting transactions. Records of those who had possessed the products in a specific lot would show how many units were received and how many were shipped, revealing, for instance, when more units were shipped by an entity than they had received or vice versa, (i.e., receipts by a wholesaler from legitimate sources were less than the disbursements to downstream partners). This is similar to the DEA batch reconciliation that is expected of the supply chain to help detect shrinkage of controlled drugs or list 1 chemicals.

In addition, under the RxTEC proposal, unit level serialization and the manufacturer's database could also be used by regulators, law enforcement or the supply chain to help identify and remove suspect product from the supply chain by comparing serial numbers to the manufacturer's database. Using the RxTEC system, certain transactions (lateral purchases, returns, etc.,) could also be verified at the unit level using the manufacturer's database.

7. **In your testimony you state that the RXTEC system would improve the efficiency and effectiveness of drug recalls. Can you please explain how lot level tracing will improve the efficiency and effectiveness in the instance of a recall?**
As noted above, by capturing the serialized RxTEC data, wholesalers will have records of particular lots of product and specific quantities sold to particular customers. Thus, in the event of a recall, wholesalers would know what customers they had shipped a particular lot to, the quantity of that shipment, and have means to enable their customers to understand whether they had ever received the particular lot being recalled. Currently, during a product recall, manufacturers can supply details regarding where the manufacturer shipped specific lots, however wholesale distributors cannot always provide details regarding the next recipient in the distribution chain because they do not always receive or track the lot data electronically from manufacturers, and typically do not capture lot numbers in their shipments to downstream trading partners. Using the RxTEC data carrier allows pharmacists and wholesalers an efficient

means to account for the recalled product. Rather than asking numerous customers "if" they received a particular recalled lot, the wholesaler can tell the customer with certainty that they received a recalled lot and the quantity they received. This is a paradigmatic improvement in supply chain security that will make patients safer. If such a system had been in place during the recall of Heparin in 2008, accounting for the contaminated product would have been much more efficient and precise.

8. **I happen to believe that manufacturers, distributors and dispensers should keep accurate and thorough records detailing who is buying and selling a drug throughout the distribution chain. Do you agree that each entity in the supply chain – manufacturers, wholesale distributions, dispensers – should be accountable for the authenticity of their product? Yes or no.**
   Yes.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED TWELFTH CONGRESS

Congress of the United States
House of Representatives

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April 11, 2012

Mr. Allan Coukell
Director
Medical Programs
Pew Health Group
901 E Street, N.W.
Washington, D.C. 2004-2008

Dear Mr. Coukell:

Thank you for appearing before the Subcommittee on Health on March 8, 2012, to testify at the hearing entitled "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain."

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 then (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions by the close of business on Tuesday, April 25, 2012. Your responses should be e-mailed to the Legislative Clerk, in Word or PDF format, at Carly.McWilliams@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

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April 20, 2012

The Honorable Henry Waxman

Response to questions for the record following the March 8, 2012 Energy and Commerce Subcommittee on Health hearing entitled: "FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval, Medical Gas, Antibiotic Development and Downstream Pharmaceutical Supply Chain."

Questions:

1. **Mr. Coukell, you mentioned in your testimony that the Pharmaceutical Distribution Security Alliance proposal includes affixing a serial number to each individual drug unit, but excludes aggregation of serial numbers. You also spoke of the need for unit level traceability, rather than simply tracing back to the lot as proposed by the PDSA. You also mentioned that the PDSA proposal does not require products to be verified for authenticity in the supply chain, meaning that there is no check for counterfeit or diverted drugs. I would imagine that such an approach could cost considerably more than lot level tracing. Can you provide information further explaining how serial number aggregation and verification are different from the current PDSA proposal, and how a company would implement and operationalize systems to incorporate these enhanced abilities that you described? Could you also provide the Committee with information that would address the costs of unit level tracing, particularly in comparison with that for lot level tracing.**
2. **Mr. Coukell, in your testimony, you spoke of the need for unit level traceability, rather than simply tracing back to the lot as proposed by the Pharmaceutical Distribution Security Alliance. I would imagine that such an approach could cost considerably more than lot level tracing. Could you provide the Committee with information that would address the costs of unit level tracing, particularly in comparison with that for lot level tracing, and that would explain how such tracing might work.**
3. **Can you explain further how serial number aggregation and verification are different from the current PDSA proposal, and how a company would implement and operationalize systems to incorporate these enhanced abilities that you described? Could you also provide the Committee with information that would address the costs of unit level tracing, particularly in comparison with that for lot level tracing, and that would explain how such tracing might work**

Dear Ranking Member Waxman,

We thank you for the opportunity to provide additional information to inform your deliberations on policies to secure drug distribution. As we discussed in our testimony, unit-level tracking and authentication of drugs is necessary to catch counterfeits and to have meaningful knowledge of the movement of medicines during distribution. The first step to achieving this, unit-level serialization, is part of the Pharmaceutical Distribution Security Alliance's proposal. The second, critical step,

aggregation, is not. Aggregation is the association of a drug unit's serial number to the case it is shipped in. It allows businesses or regulators to know the distribution path of individual drug units. Tracking at the lot-level would not allow this. A drug lot – the level at which the PDSA proposes to track medicines – includes thousands of drug units packed in dozens of cases that are shipped to numerous different wholesalers and pharmacies. It is entirely possible for a single wholesaler or pharmacy to have shipments of the same drug lot procured through different distribution pathways.

The PDSA has already committed to bear the cost of serializing drugs at the unit level. Regarding the additional cost of aggregation borne by industry, we would like to direct you to a statement prepared by Walter Berghahn, President of SmartRMeds For Life and Executive Director of The Healthcare Compliance Packaging Council. Mr. Berghahn has worked for over 25 years in the packaging and pharmaceutical industries. His statement, attached herewith, focuses on the affordability and benefits of serialization with aggregation.

Key points in this document include:

- Some pharmaceutical manufacturers have already taken steps to enable unit-level tracking of their products. Unit-level tracking would not require the pharmaceutical industry to develop new or complex technologies. Rather it would involve the adoption and repurposing of existing technologies. Most packaging liens today already make use of similar equipment and technologies.
- The major cost for unit-level tracking is the cost of attaching serial numbers to individual packages. Moving to serialization alone already represents 56%-77% of total cost to equip a production line for unit-level tracking.
- The additional investment to achieve aggregation will reduce patient safety risks and will provide financial benefits to the company. Supply chain visibility with unit level tracking would reduce the likelihood of counterfeits, product diversion, and gray market activity, and would allow for targeted recalls and returns reconciliation. Similar reductions cannot be achieved using the lot level approach.

If there is any additional information we can provide you, please do not hesitate to contact me at (202) 540-6392 or acoukell@pewtrusts.org.

Sincerely yours,

Allan Coukell
Director of Medical Programs
Pew Health Group
The Pew Charitable Trusts

Written Statement for the Record
Walter Berghahn
President, SmartRMeds For Life
Executive Director, The Healthcare Compliance Packaging Council
Before the
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

On the
Practicality and Affordability of Aggregating Pharmaceutical Products at the Unit Level on Packaging Lines

March 8, 2012

Walter Berghahn, President of SmartRMeds For Life and Executive Director of The Healthcare Compliance Packaging Council, is grateful to the Committee for considering his comments as it examines measures to secure the drug distribution system.

Walter has worked for over 25 years in the Packaging and Pharmaceutical industries. He offers a unique perspective on the needs of drug manufacturers and patients due to his intimate knowledge of drug packaging and his broad range of experiences throughout the supply chain. Walter's previous projects have focused on: Track and Trace, pedigree, serialization, institutional use of packaging (from hospitals to long-term care), automation integration, electronics integration in packaging, and patient adherence monitoring.

Executive Summary

This written statement is intended to explain that serialization and tracking at the unit level is practical and affordable for the pharmaceutical industry, as demonstrated by millions of transactions taking place on a daily basis in other industries.

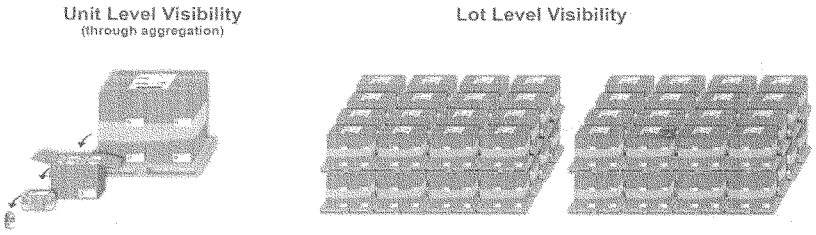
Unit level tracking is the only practical way to improve supply chain visibility of individual units which can reduce instances of counterfeiting, diversion and unsafe prescription drug activities. Unit level tracking with bar code serialization is best accomplished through the process of aggregation, whereby multiple containers of like drugs are grouped into larger cases for distribution in the supply chain. The serialized case ID's relate to the serialized unit ID's (parent / child relationship) in data which is only visible to targeted supply chain partners through secure business transactions. Diverted product will show up "out of position" in the supply chain and counterfeiters will not know the numbering scheme nor where the serialized containers were sold making it virtually impossible to introduce product in the legitimate supply chain.

Pharmaceutical manufacturers regularly use bar coding in current process. Each unit of saleable product must have the NDC (National Drug Code) present on the container in Code 128 format. What the California law (SB 1307) is doing is simply requesting to modify that form to a 2D data matrix code which can handle more data and hold a serial number for each unit in the market making them truly unique and therefore traceable in the supply chain. Many manufacturers can repurpose existing equipment on their packaging lines to upgrade for unit level serialization. Cost estimates will vary depending on the company's serialization solution. **Manufacturers can expect to pay from $364,000-$640,000 for the necessary line equipment, software & data configuration, and implementation costs.** These cost estimates are for a manufacturer to retrofit its first packaging line for serialization with aggregation capability. Subsequent lines would be less expensive. It is important to note that an upgrade for unit-level serialization without aggregation would be 56%–77% of these estimates. Therefore companies serializing product will already cover the majority of costs. The smaller additional investment to achieve aggregation not only will provide financial benefits to the company but will reduce risks to patient safety.

Overview and Existing Technology

Industry and regulatory organizations have been considering a serialization and traceability system for years. Most proposals involve serializing drug products at the smallest saleable unit. Among these, there are two opposing approaches regarding how drugs should be tracked:

- **Unit serialization with required tracking at the *unit* level.** This approach would enable supply chain visibility from the pharmacist back to the manufacturer for every discrete saleable drug product. The California e-Pedigree law, as well as other proposals federally advanced, would require this approach.
- **Unit serialization with required tracking at the *lot* level.** This approach would provide supply chain visibility between the manufacturers and distributors for every pharmaceutical product lot. These lots can vary in size and represent hundreds of thousands of different drug products created over long stretches of time. Pharmacists, however, would not be required, and in most cases would not be able to, authenticate an individual drug product.



Unit level serialization and tracking would not require the pharmaceutical industry to develop new or complex technologies. Rather, it would involve the adoption and repurposing of existing technologies to protect consumers of drug products.

Further, several industries already depend on the ability to track and authenticate millions of unique IDs daily. Retail stores and warehouses across America have been using a parallel technology, barcode scanning, for decades to manage their inventories. Even hospitals, including the VA, rely on barcodes to properly administer medications.

Express delivery industry tracks over 23 million serialized units per day

In 2011, the two biggest express delivery companies in the U.S. (Fed Ex, UPS) shipped, on average, a combined daily total of 23 million units, all of which relied on serialization and tracking technologies.

Credit card industry authenticates over 64 million transactions per day

Estimates show that credit card companies authenticate approximately 64 million credit card transactions daily. This estimate excludes account transactions for debit and ATM cards. Each card swipe is authenticated in real time via secure databases.

The California law, if applied federally, would require pharmacies to track and authenticate 11 million prescriptions per day

Pharmacists scan drugs at the unit level every day. The vast majority of U.S. pharmacies use a bar code scanner to read the National Drug Code (NDC) number, which is on every saleable unit. Also, pharmacies use bar codes on prescriptions to identify patients in their databases and to link prescribed products to the actual prescriptions.

Further, national figures, on average, show that independent pharmaceutical stores fill 200 prescriptions per day, while large retail chains fill about 300 per day. Adding serialized containers to

this process would not involve additional scans. Rather pharmacists would substitute one type of scan (NDC) for another (SGTIN), which may require upgrading or modifying scanning equipment.

Supply Chain Visibility With Unit Level Tracking

Supply chain visibility with unit level tracking would reduce the likelihood of counterfeits, product diversion, and gray market activity, and would allow for targeted recalls and returns reconciliation. Similar reductions cannot be achieved using the lot level approach.

Aggregation – the process of grouping similar units into larger packages – is the most efficient and cost effective means of providing unit level visibility to products as they move through the supply chain. Aggregation involves creating a unique serial number at each level of packaging to establish parent-child relationships. This way, individual drug units can be identified regardless of how many layers of packaging the unit is encased in.

Most of the arguments for and against unit level tracking are centered on cost. However, lost in this discussion are some of the opportunities that would improve patient safety:

Optional Home Authentication

Unit level tracking opens the door to home based drug authentication. In the future, patients or caregivers could gain peace of mind by scanning a serialized drug unit (with their phone or other scanning device). In theory, an individual could verify that his or her drug indeed came from the pharmacy from which it was purchased and that the drug has a complete and valid chain-of-custody record going all the way back to the manufacturer.

Better Supply Chain Management

Unit level serialization and tracking are the first steps to a safer drug supply chain. Only when stakeholders better understand where and how drugs travel through the supply chain, can they begin monitoring what happened to the drugs during transit. For example, supply chain managers could monitor storage history and transit conditions relative to changes in temperature, which can directly affect drugs' efficacy.

Affordable aggregation solutions for unit level tracking, using proven technologies, exist and can contribute significantly to the safety of consumers and the security of the U.S. pharmaceutical drug supply chain.

Coding Technology and Aggregation In Use Today

There is broad consensus across the pharmaceutical industry that the preferred and most cost-effective means of unit level tracking involves printed 2D data matrix codes. A common argument against unit level tracking is that companies would need to introduce new equipment, which would be too expensive to implement. Most packaging lines, however, are using, and have been using for decades, similar equipment and technology, which includes:

- Printers and coding equipment
- Cameras and inspection equipment
- Reject systems
- Labeling equipment
- Sensors and automation controls

Repurposing existing equipment, when possible, to print and inspect unique codes would allow pharmaceutical companies to serialize at the unit level and comply with the California law. Also, unit level serialization would enable companies to pursue, at their own discretion, additional equipment to monitor drug units as they get aggregated (into a bundle, case, pallet, etc).

Machinery manufacturers are already providing pharmaceutical companies with unit level tracking and aggregation solutions. For example, in 2009, a mid-Atlantic pharmaceutical company sought to manage risks to its internal supply chain. The client worked with a machinery manufacturer to print unique, human-readable codes on the bottom of every bottle. With these codes, the client was able to establish high integrity, parent-child relationships between the case and bundle labels, and the individual bottles.

Currently, the same machinery manufacturer is delivering a custom, end-of-line solution for three carton lines to one of its major pharmaceutical clients with operations in China. The operation involves a unique code being applied to the sides of every carton. The cartons are aggregated, first into a bundle and then into a case. At each level of aggregation, a package receives a unique serialized label that identifies all its constituent cartons.

There are numerous examples of aggregation solutions being deployed across the Pharmaceutical industry, as well as aggregation solutions currently operating in the Automotive, Computer, and Personal Care industries.

Estimated Costs to Upgrade Existing Packaging Lines for Serialization

Unit Level Serialization with Aggregation

Current estimates, from several notable manufacturers and suppliers, indicate that a company will pay from $364,000-$640,000 to retrofit its first packaging line with unit level serialization and aggregation. These figures include one-time expenses, general infrastructure costs, and software licensing fees, all of which a company can leverage to substantially reduce the cost of adding subsequent lines within the same facility.

The vast majority of pharmaceutical products fall into two primary categories: round bottles (solid oral dose and liquids) and cartons (blister packs, vials, syringes, etc). The following cost estimates consider both of these packaging formats under two different upgrade scenarios.

	Low-Complexity Packaging Line Serialization Upgrade	**High-Complexity Packaging Line** Serialization Upgrade
Line Equipment	$70,000	$212,000
Data Servers & Software Configuration	$190,000	$245,000
Implementation	$104,000	$183,000
Unit Level Serialization Upgrade	$364,000	$640,000

* Costs shown are for the initial packaging line

These figures factor in validation, project management, and contingency factors (at 40% of the supplier costs). These costs do not factor in additional serialization expenses at the enterprise level.

The wide cost range reflects two extreme scenarios and should not be interpreted as either-or. Most manufacturers will incorporate aspects from each scenario, depending on the complexity level of their serialization solutions and the availability of existing equipment.

Unit Level Serialization without Aggregation

Companies can forego the inclusion of aggregation in their unit level serialization solution, but an upgrade to serialization alone would already represent the majority of costs estimated here: 56%–77%. (The additional amount to aggregate is due to some Line Equipment and Implementation costs that are associated with aggregation. The Data Servers & Software Configuration costs would remain the same.) Because there is broad agreement that unit level serialization will become an expectation of our distribution system, I strongly advise that the smaller additional investment to achieve aggregation is well justified. Companies will see financial benefits, and risks to patient safety will be reduced.

Serialization Upgrade Scenarios

Low-Complexity Packaging Lines

This scenario considers companies with lines that are running at low-speed, low-volume. This scenario assumes a company is serializing a simple product (rectangular carton) with manual packing with two levels of aggregation (cartons into cases; cases onto pallets). Here, the serialization upgrade would consist mostly of software modifications to existing labeling equipment. The company would need to purchase some additional cameras and inspection stations and obtain software licenses.

Each unit (carton) would receive a serialized code at the labeling station. The units would travel downstream, ultimately reaching the case packing station. Inspection equipment would scan the serialized unit codes, layer by layer, as the units get loaded into a case having its own serialized label. Once the final layer is loaded and scanned, the case gets sealed, which establishes the parent-child relationship between the case and its constituents. The case would then be scanned and manually placed on a pallet having its own serialized label establishing that next level of aggregation. Each step in this scenario takes advantage of existing packaging operations and label stock requirements with slight modifications.

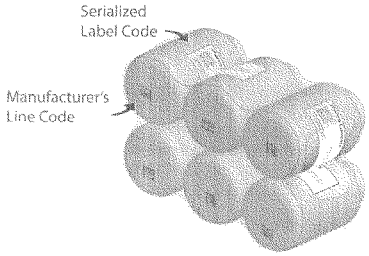
Necessary purchases and upgrades:

- Modify existing labeling equipment for serialization
- Install additional inspection equipment to read serialized codes
- License, implement, and maintain a data management system

High-Complexity Packaging Lines

This scenario considers companies with high-speed, high-volume operations that seek robust tracking of their products throughout a packaging line. This scenario assumes a company is serializing a challenging product (round bottles) with several levels of aggregation (bottles into bundles; bundles into cases; cases onto pallets).

Each unit (round bottle) would get a unique manufacturer's line code printed either on its cap or its bottom. The line code is relevant only to the packaging line and for processing and forensic use. The line code is distinct from the serialized label code (sGTIN), which a pharmacist or other supply chain partner could scan, and which would get applied to the unit further down the packaging line.



Immediately after the serialized label is applied to the unit, custom inspection equipment would synchronize the label with the manufacturer's line code. The units would travel down the packaging line with two unique codes towards a bundling station, which would group and shrink wrap several units into small bundles. A labeling station would apply a unique serialized label to the bundle.

It is important to note that the serialized label codes on round bottles may be blocked or hidden from an inspection camera when the bottles are grouped. However, the manufacturer's line codes would still be visible (on the units' caps or bottoms). Inspection equipment would simultaneously scan the bundle's label code and manufacturer's line codes on all the units to establish the parent-child relationship.

Upon reaching the automatic case packer, each layer would be scanned, either looking for bundle labels or the manufacturer's line codes, while the scanner simultaneously reads the serialized case label. In this manner all layers of bundles would be aggregated to the case establishing the second level of parent-child aggregation.

Lastly, after exiting the case packer, cases would be automatically palletized. A scanner would read the case codes while another system (scanner or RFID reader) simultaneously reads the serialized pallet code (either 2D data matrix or RFID tag), establishing the third and final layer of parent-child aggregation.

The equipment described below provides the highest level of integrity since it enables companies to establish the parent-child relationship *after* the serialized aggregation takes place.

Necessary purchases and upgrades:

- Modify existing labeling equipment for serialization
- Install line printing equipment to place manufacturer's line code on bottle and label on bundle
- Install additional inspection equipment to read serialized codes
- Install post-labeler station to sync the manufacturing and serialized code
- Install end-of-line inspection station and modifications to case packer and palletizer
- License, implement, and maintain a data management system

Summary

Unit level serialization and tracking technology, which is needed to satisfy the California e-Pedigree law, is available and is being managed successfully in other industries. The pharmaceutical industry can realize high-integrity serialization solutions by repurposing or upgrading existing equipment.

For pharmaceutical manufacturers, the cost to upgrade a packaging line for serialization varies relative to the complexity of the company's solution. Nevertheless, affordable options exist.

Unit level serialization, aggregation, and tracking provide many financial benefits. However, the pharmaceutical industry as a whole should make unit level tracking a moral imperative considering the immense benefits it would bring to patient safety.

Resources

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