

**FDA USER FEES 2012: HOW INNOVATION HELPS
PATIENTS AND JOBS**

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

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FDA USER FEES 2012: HOW INNOVATION HELPS PATIENTS AND JOBS

WEDNESDAY, APRIL 18, 2012

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

The Subcommittee met, pursuant to call, at 10:15 a.m., in room 2123 of the Rayburn House Office Building, Hon. Joe Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Rogers, Myrick, Murphy, Blackburn, Gingrey, Latta, Lance, Cassidy, Guthrie, Barton, Bilbray, Upton (ex officio), Pallone, Dingell, Engel, Capps, Schakowsky, Matheson, Eshoo, Markey, and Waxman (ex officio).

Staff present: Clay Alspach, Counsel, Health; Gary Andres, Staff Director; Nancy Dunlap, Health Fellow; Paul Edattel, Professional Staff Member, Health; Debbie Keller, Press Secretary; Ryan Long, Chief Counsel, Health; Carly McWilliams, Legislative Clerk; Monica Popp, Professional Staff Member, Health; Chris Sarley, Policy Coordinator, Environment and Economy; 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.

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

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

Today's hearing addresses the FDA user fee package discussion draft. This draft is the product of over a year of hard work by various parties. While the individual industries—prescription drugs, medical devices, generic drugs and biosimilar drugs—represented in this draft were negotiating with FDA on their user fee agreements, this subcommittee was holding at least 10 hearings on subjects related to the draft. After intense negotiation between both sides of the aisle, we have arrived at a discussion draft that I hope all members of the subcommittee will be able to support.

There are still some outstanding issues that staff continues to work on, and I hope that they can be resolved before next week's subcommittee markup.

This package is critical to patients. It will ensure that FDA has the resources and reforms needed to speed new drugs, devices and treatments to those who are ill. These user fee agreements will make the approval process more transparent, more consistent and more predictable, benefiting patients, but also keeping the United States the preeminent leader in drug and device development and manufacturing.

Good-paying jobs in the drug and device industries, like those in my home State of Pennsylvania, will be critical to our economic recovery, and we cannot afford to outsource them.

I look forward to hearing from our witnesses today, to get their thoughts and reactions on the discussion draft.*

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

Today's hearing addresses the FDA user fee package discussion draft. This draft is the product of over a year of hard work by various parties. While the individual industries—prescription drugs, medical devices, generic drugs, and biosimilars drugs—represented in this draft were negotiating with FDA on their user fee agreements, this Subcommittee was holding at least ten hearings on subjects related to the draft.

After intense negotiation between both sides of the aisle, we have arrived at a discussion draft that I hope all members of the Subcommittee will be able to support. There are still some outstanding issues that staff continues to work on, and I hope that they can be resolved before next week's Subcommittee markup.

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I look forward to hearing from our witnesses today, to get their thoughts and reactions on the discussion draft.

Mr. PITTS. I yield the remaining time to the chairman emeritus of the committee, Mr. Barton.

OPENING STATEMENT OF HON. JOE BARTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BARTON. Thank you, Mr. Chairman, and thank you for holding this hearing today.

Put me down, as I said at the last hearing you had on this, as undecided on this particular bill. I know that you have worked very hard and your staff has worked very hard and the minority staff and members have worked very hard on the bill. My basic problem is that I am not sure the FDA deserves a large increase in user fees given the amount of money that they have been receiving in general fund increases.

As you know, under the Patient Protection and Affordable Care Act, there is a new 2.3 percent gross sales tax on the sale of all medical devices in the United States beginning in the year 2013. This tax is supposed to raise \$20 billion to help offset the cost of

*The discussion draft is available at <http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/Hearings/Health/20120418/BILLS-112HR-PIH-UFAreauthorization.pdf>.

President Obama's \$1 trillion new health bill. A 2.3 percent tax is imposed on revenues, as you know, and not profits, so that the tax applies to devise regardless of they are sold at a loss. This is on top of the current federal tax rate of 35 percent on corporate profits and all State and local taxes in addition. It is obvious that companies have less incentive to stay in the United States than they did before these bills became law.

This Administration has indicated that the increased tax will have little to no negative effect on medical innovation in the United States. That just begs credulity, Mr. Chairman. When you increase taxes across the board and then throw these user fee increases on top of it, that has to have a negative effect. It is simply a law of physics, so to speak.

In any event, I do want to commend you and others for trying to come together on a bipartisan bill. I think it is obvious by my comments that I may be a no vote but I do want to be a positive part of the process if at all possible.

I want to thank our witnesses for being here today, and with that, Mr. Chairman, I can yield the remaining 1 minute to someone else or yield it back to you.

Mr. PITTS. All right. The gentleman yields back. The chair recognizes the ranking member of the Subcommittee on Health, Mr. Pallone, for 5 minutes.

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

Mr. PALLONE. Thank you, Chairman Pitts.

Today, the subcommittee is meeting to hear testimony about the released discussion draft concerning the prescription drug, medical device, generic drug and biosimilar drug user fee agreements as well as several other FDA-related proposals including programs to foster the development of prescription drugs for children, administrative and regulatory reforms at the FDA, and drug shortages.

I will note as a matter of process that each of these issues has had its own hearing in the subcommittee over the course of the 3 months, and I want to commend Chairmen Pitts and Upton and the staffs on both sides. We have worked very hard to cover a lot of ground, and I would also like to thank all the subcommittee members for their participation in these hearings and I welcome their comments and suggestions on the discussion draft as we continue to move forward.

Let me state that we have not yet reached full agreement on the discussion draft in time for today's hearing. As we will be seeing, the bill contains language largely identical to the March draft released by the Republicans except for the brackets surrounding a majority of the text. These brackets indicate that the bill is a work in process and we continue to make headway.

There are many issues that have been worked out. Specifically, we have been able to make substantive changes to the FDA reforms in this draft would have led to many unintended and unacceptable consequences to FDA's regulatory scheme. We have also been working hard to include language that would equip the FDA with the authority and the resources it needs to address a growing

global drug supply. That language has come a long way, and I am optimistic that we can strengthen it further.

It is important to note that there are still key concerns remaining but the process has been a good one to date and I am hopeful that we can come together to address those outstanding issues and generate a consensus, a bipartisan product that both sides can support.

I just wanted to quickly comment on the four user fee proposals that are the impetus behind this legislation. The discussion draft is largely based on the agreements between the FDA and the industry. These programs represent a critical opportunity to work alongside FDA, industry and other stakeholders to build upon and improve these critical programs. Together we can help give patients access to safe, effective and breakthrough medical treatments while supporting the advancement of science and promoting a thriving life science industry in the United States.

A particular note of course is the new generic drug user fee agreement, which will dramatically improve the median approval times for generic applications. This program will cause an influx of generic drug products onto the market and into the hands of consumers, thereby significantly lowering health care costs.

I just want to welcome back our witnesses here today. You have been a great resource to our subcommittee throughout this process. We are eager to hear your opinions and your suggestions, and I look forward to working with you, Chairman Pitts, leading up to next week's scheduled markup to improve the discussion draft further. And again, thanks for the continued bipartisanship.

I would like to yield my 2 minutes left to the chairman emeritus, Mr. Dingell.

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

Mr. DINGELL. Mr. Chairman, I thank you for holding today's hearing and I thank my good friend, Mr. Pallone, for yielding to me.

I am delighted that we are having this hearing and I am happy to work together with my colleagues in a bipartisan consensus effort to achieve a good piece of legislation on food and appliance and other performance by the FDA.

FDA's authorities are not sufficient to protect our drug supply chain. Investigations by this committee found the FDA not only lacks knowledge of how many drug manufacturing facilities are operating overseas, what entities are importing drugs or when incidents like adulteration, theft, counterfeiting, contamination or repeated manufacturing failures are posing health risks. FDA has lacked the authority to detain or destruct harmful drugs, to prevent medical product from entering the country if the manufacturer prohibits inspection or to require importers to provide compliance information at the border.

Current law has unintentionally created an unlevel playing field which hurts our domestic manufacturers. While FDA inspects domestic manufacturers every 2 years, it may or may not inspect foreign manufacturing facilities, although it occasionally gets around

to it about every 9 years. This committee must address these critical gaps in FDA's authority and the knowledge of our entire food chain from active ingredients to the patient's medicine cabinet. FDA ought to know the parties who are manufacturing, distributing or importing drugs and should be able to take action against those who are allowing harmful drugs into the United States market.

We have before us today an opportunity to deal with the shortage of money and personnel and see to it that we stop making Americans sick or killing Americans by having a failure to have Food and Drug have the ability to carry out its responsibilities. I thank you, Mr. Chairman.

Mr. PITTS. The gentleman yields back, and I now recognize the chairman of the full committee, Mr. Upton, for 5 minutes.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Thank you, Chairman Pitts, for today's hearing on the reauthorization of the FDA user fees and the impact of innovation on American patients and jobs.

Since the beginning of February, this subcommittee has held six hearings on the FDA, and during these hearings, we have heard from witnesses from around the country on how Congress can help FDA become more predictable, consistent and transparent and how that will foster innovation here in the United States. I have heard this back home from my constituents as well. I think we all agree that fostering innovation does help American patients and aids in creating American jobs. As part of our efforts to foster that innovation, we need to fix the recent problems with the investigational device exemption approval process and the medical device modifications guidance document. Recent FDA policy changes have created some problems, and we intend to use the user fee legislative process to rectify them.

I really want to thank Mr. Waxman and Mr. Pallone and Mr. Dingell and other members of this committee for their constructive and bipartisan work to reauthorize these user fees. During the past couple of months, we have had a number of productive conversations on ways to improve the regulatory process at FDA. As I said at the start of this process, we need to reauthorize the user fees by the end of June to assure continuity at the FDA and increase predictability for America's medical innovators and job creators. We still have work to do but because of the bipartisan commitment from members on both sides of the aisle, I am convinced that we are on track to do that, and I appreciate all the hard work, particularly from the staff as they have spent countless numbers of hours working to make sure that we can have a productive bill, and I yield the balance of my time to the vice chairman of the subcommittee, Dr. Burgess.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

I'd like to thank Chairman Pitts for holding today's hearing on the reauthorization of the Food and Drug Administration user fees and the impact of innovation on American patients and jobs.

Since the beginning of February, this subcommittee has held six hearings on the FDA. During these hearings, we've heard from witnesses from around the country on how Congress can help FDA become more predictable, consistent and transparent and how that will foster innovation here in the United States. I have heard this back home from my constituents too.

I think we all agree that fostering innovation helps American patients and aids in creating American jobs. As part of our efforts to foster innovation, we need to fix the recent problems with the investigational device exemption approval process and the medical device modifications guidance document. Recent FDA policy changes have created major problems, and we intend to use the user fee legislative process to rectify them.

I'd like to thank Ranking Member Waxman, Ranking Member Pallone, Mr. Dingell and the other Democratic members of the Energy and Commerce Committee for their bipartisan work on reauthorizing the user fees. During the past few months, we've had productive conversations on ways to improve the regulatory process at FDA.

As I said at the start of this process, we need to reauthorize the user fees by the end of June to assure continuity at the FDA and increase predictability for America's medical innovators and job creators. We still have work to do but because of the bipartisan commitment from members on both sides of the aisle, we are on track to do that.

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

Mr. BURGESS. I thank the chairman for yielding. I want to thank the chairmen of the full committee and subcommittee as well as the ranking members of the full committee and subcommittee for moving this legislation forward. I think the manner that this has been approached is one that has been constructive and certainly been respectful of individual member concerns. We have been sensitive to patient concerns and we are focused on finding an end product that is workable for the agency and for the patients that it serves.

The impact of these areas, the medical device, the pharmaceutical, the biologic and generic industries of the United States certain reaches farther than the patients that benefit from them, and we will hear a lot about job creation and help to the economy, but the patient concerns must remain our primary focus. And these industries do affect commerce. They affect technology. They do affect the economy and they provide quality jobs to Americans, which range from the scientific to the highly skilled and technical and those involved in their manufacturing.

The Food and Drug Administration has one of the most important missions of any federal agency to ensure that medical products are safe and effective. They are also the gateway to providing patients with products that help them maintain their health, perhaps help them live with a chronic condition. We have to be certain that that gateway does not become a bottleneck. I think there are constructive updates that can be made and I appreciate so much the discussion draft now being out there for all of us to reflect and offer our thoughts.

Again, I want to thank the chairman for his approach to the process, thank our witnesses for their willingness to come before this committee multiple times, for the transparency that they have exhibited and the fact that this has come through under regular order and that the chairman has worked to a product which I think both sides of the dais can justifiably be proud, and I—

Mr. SHIMKUS. Will the gentleman yield?

Mr. BURGESS. Yes, I will be happy to yield.

Mr. SHIMKUS. Thank you. I want to just take a minute and talk about this process and some of the reforms that are proposed and just make the point, especially in two areas that I have been interested in, the investigative device exemption and the 510(k) modifications.

The attempt is really to remedy through public policy changes in the operation that the FDA has done in the last couple years. So it is an attempt to return back to a day when these two areas were working and we weren't losing innovation and jobs and folks moving overseas to get these approvals. And so I hope that you all will when we get into that part of the discussion receive it in the attempt that we are trying to portray it. We really want to get back to where we don't have this backlog and we are the innovators, we are the producers and we lead the world again.

I yield back my time.

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

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

Mr. WAXMAN. Chairman Pitts, thank you for holding this hearing today.

Although we were not able to come to full agreement in time for the discussion draft released yesterday, I am pleased with the progress that we have made on this user fee package thus far. I am optimistic that we will get to full agreement soon. We all know how important it is to reauthorize the underlying user fee programs in a timely way. No one is served by adding controversial proposals to the bill. That would only serve to slow the process.

So far, we have worked together to avoid weighing down this critical legislation with extraneous policies about which we cannot agree. This will ensure that we get the work on these critically important bills done in time.

I am particularly hopeful about the progress we have made in the area of drug safety as it relates to the increasingly globalized supply chain. Mr. Dingell has a strong bill that has served as a template in this area, and I appreciate all the work that Mr. Upton and Mr. Pitts have done to incorporate provisions modeled on that bill.

I want to note however that I continue to have strong concerns with respect to devices. We have all heard the increasing rhetoric that FDA is slowing innovation and forcing jobs abroad, but that does not justify the troubling provisions that could compromise patient safety that are under consideration. There are numerous examples of unsafe medical devices that have been permitted on the market and have caused incalculable suffering for victims. And that occurs under the current system with the powers FDA has today. Now is not the time to go backwards and take away important authorities from the FDA that it needs to help ensure the safety and effectiveness of devices. I will continue to oppose any ad-

dition of any provisions that would prevent FDA from doing what it feels necessary to protect patients from unsafe and ineffective devices.

Let me turn now to the area of antibiotics. The discussion draft includes the GAIN Act, which is a good first step toward creating incentives for the development of new antibiotics, which we all agree we desperately need. I remain concerned that the bill does not narrowly target antibiotics that treat dangerous infections for which we don't have adequate treatments. The bill should also include provisions to ensure that the efficacy of these newly developed antibiotics is preserved once they are on the market. These are goals we should all share and I am optimistic that we will fix the bill to achieve them.

I also look forward to learning more today about the proposal put forward by the Infectious Disease Society of America, the Limited Population Antibacterial Drug, or LPAD—it sounds like a new technical device sold by Apple—approval mechanism. This proposal would establish a more rapid regulatory pathway for new antibiotics targeted at the most serious infections.

The concept appears to have great promise at speeding important new antibiotics to the market, but I think we need to be assured that these drugs will not be inappropriately used. If we cannot get that assurance, we should all be concerned about moving forward with this kind of proposal.

Strengthening and improving FDA is in the interest of all Americans. I look forward to continuing to work with all of my colleagues on this committee to reach bipartisan agreement on this critically important legislation, and I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman.

We will now go to panel one. We have two panels today. Our first panel will have two witnesses: Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA; and Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health. We are happy to have both of you here today.

Dr. Woodcock, you are now recognized for 5 minutes for your opening statement.

STATEMENTS OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION; AND JEFFREY E. SHUREN, M.D., J.D., DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

STATEMENT OF JANET WOODCOCK

Dr. WOODCOCK. Thank you. Mr. Chairman, members of the subcommittee, thank you for the opportunity to testify about the three important drug user fee proposals that are laid out in the discussion draft. Each of three drug user fee programs is important for the public, and will, if enacted, impact positively on patients, industry and on biomedical innovation.

The fifth iteration of the prescription drug user fee program contains important advances for regulatory science and patient-centered drug development as well as maintaining consistent and predictable review process for the innovator industry. The biosimilars

user fee program will support the growth of a new industry and will help provide more affordable biological drugs to the public. Both I think are very important public goals.

The generic drug user fee program as proposed would represent a historic agreement to maintain a high and uniform level of drug quality no matter where the drug is sourced in the world. It also will ensure a robust and predictable path to market for generic drugs that should invigorate the industry.

That said, implementation of these three new programs if enacted will create a significant body of work for the agency. We are eager to undertake this but we are wary of additional provisions, unfunded provisions. The experience after the FDA Amendments Act I think is illustrative. While FDA implemented the many needed safety programs that were stipulated in the Amendments Act, we had to miss a number of user fee goals under the prescription drug user fee program and slow down our review process, and while that was a worthy tradeoff, we have to recognize that any additional provisions will have tradeoffs on workload.

I understand that there are other policy issues and development challenges that are unaddressed by the user fee proposals, which are really about process and procedures, and I am happy to answer questions about these issues and I really look forward to the discussion. Thank you.

[The prepared statement of Dr. 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

COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH

U.S. HOUSE OF REPRESENTATIVES

"FDA USER FEES 2012: HOW INNOVATION HELPS PATIENTS AND JOBS"

April 18, 2012

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA),¹ also referred to as PDUFA V, as well as the negotiated recommendations for a generic drug user fee program and a biosimilar user fee program. I will also discuss a number of other important issues facing FDA, including expediting access to new therapies, the renewal of legislation to promote pediatric drug testing, securing the supply chain for prescription drug products, the regulation of medical gases, efforts to facilitate the development of antibacterial drug products, as well as update you on actions the Agency is taking to address the ongoing problem of drug shortages.

Background on PDUFA

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. Prior to enactment of PDUFA in 1992, FDA's review process was understaffed, unpredictable, and slow. FDA lacked sufficient staff to perform timely reviews, or develop procedures and standards to make the process more rigorous, consistent, and predictable. Access to new medicines for U.S. patients lagged behind other countries. As a result of concerns expressed by both industry and patients, Congress enacted

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

PDUFA, which provided the added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. At the same time, FDA committed to complete reviews in a predictable time frame. These changes revolutionized the drug approval process in the United States and enabled FDA to speed the application review process for new drugs, without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval.

Three fees are collected under PDUFA: application fees, establishment fees, and product fees. An application fee must be submitted when certain NDAs or BLAs are submitted. Product and establishment fees are due annually. The total revenue amounts derived from each of the categories—application fees, establishment fees, and product fees—are set by the statute for each fiscal year (FY). PDUFA permits waivers under certain circumstances, including a waiver of the application fee for small businesses and orphan drugs.

Of the total \$931,845,581 obligated in support of the process for the review of human drug applications in FY 2010, PDUFA fees funded 62 percent, with the remainder funded through appropriations.

PDUFA Achievements

PDUFA has produced significant benefits for public health, providing patients faster access to over 1,500 new drugs and biologics, since enactment in 1992, 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

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.

approvals in the past 10 years, surpassed only by 2009. Of the 35 innovative drugs approved in FY 2011, 34 met their PDUFA target dates for review.

Substantially Reduced Review Times

PDUFA provides FDA with a source of stable, consistent funding that has made possible our efforts to focus on promoting innovative therapies and help bring to market critical products for patients.

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 years for the approval phase at the start of PDUFA to an average of 1.1 years more recently.²

FDA aims to review priority drugs more quickly, in six months vs. 10 months for standard drugs. Priority drugs are generally targeted at severe illnesses with few or no available therapeutic options. FDA reviewers give these 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.

Reversal of the “Drug Lag”

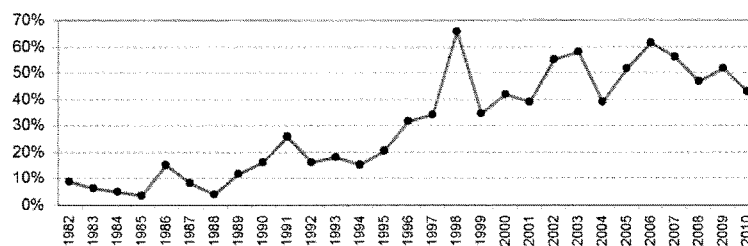
Importantly, PDUFA has led to the reversal of the drug lag that prompted its creation. Since the enactment of PDUFA, FDA has steadily increased the speed of Americans’ access to important new drugs compared to the European Union (EU) and the world as a whole. Of the 35 innovative drugs approved in FY 2011, 24 (almost 70 percent) were approved by FDA before any other regulatory agency in the world, including the European Medicines Agency. Of 57

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.

novel drugs approved by both FDA and the EU between 2006 and 2010, 43 (75 percent) were approved first in the United States.

Figure 1 below shows that since the late 1990s, the United States has regularly led the world in the first introduction of new active drug substances.³ Preliminary data show that in 2011, over half of all new active drug substances were first launched in the United States.

Figure 1. U.S. Share of New Active Substances (NAS) First Launched on the World Market



Year of NAS First Launch Worldwide

In recent years, FDA's drug review times also have been, on average, significantly faster than those in the EU. It is difficult to compare length of approvals for FY 2011, because many of the drugs approved in the United States have not yet been approved in the EU. A comparison of drugs approved in the United States and the EU between 2006 and 2010 is illustrative, however. For priority drugs approved between 2006 and 2010, FDA's median time to approval was six months (183 days), more than twice as fast as the EU, which took a median time of 13.2 months (403 days). For standard drug reviews, FDA's median time to approval was 13 months (396 days), 53 days faster than the EU time of 14.7 months (449 days).

³ Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 -2005), PharmaProjects R&D Annual Review (2006-2010). New active substances include novel chemical or biological substances not previously approved to treat any disease. There is a close, but not complete overlap, between new active substances and new molecular entities: new active substances exclude radiopharmaceuticals.

A recent article in the journal *Health Affairs* also compared cancer drugs approved in the United States and 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 only 26 of these products, and its average time was 12.2 months (373 days). This difference in approval times is not due to safety issues with these products. All 23 cancer drugs approved by both agencies during this period were approved first in the United States.⁴

Speeding Access to New Therapies

PDUFA funds help support a number of existing FDA 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 fill an unmet medical need 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

⁴ “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.

on the condition that sponsors conduct post-marketing clinical trials to verify the anticipated clinical benefit.

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) and new BLAs approved in 2011 in CDER were approved under Accelerated Approval. Corifact, the first treatment approved for a rare blood-clotting disorder, also was approved under Accelerated Approval in FDA's Center for Biologics Evaluation and Research (CBER) 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. Once a drug receives Fast-Track designation, early and frequent communications between FDA and a drug company are encouraged throughout the entire drug development and review process. The frequency of communications ensures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients. For example, Zelboraf (vemurafenib) was given a Fast-Track designation because it had the potential to improve overall survival in patients with melanoma, the most dangerous type of skin cancer. Because of convincing early findings with this drug, FDA scientists worked proactively with the sponsor during drug testing to encourage early submission of the application. FDA approved Zelboraf in 2011 to treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma.

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 of ivacaftor 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 is the first medicine that targets the underlying cause of CF; to date, therapy has 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.

Providing Guidance to Industry

Increased resources provided by user fees have enabled FDA to provide a large body of technical guidance to industry that clarified the drug development pathway for many diseases, and to meet with companies during drug development to provide critical advice on specific development programs. In the past five years alone, FDA has held over 7,000 formal meetings with drug sponsors within a short time after a sponsor's request. Innovations in drug development are being advanced by many new emerging companies as well as more established ones, and new sponsors may need, and often seek, more regulatory guidance during development. In FY 2009 through FY 2011, more than half of the meetings FDA held during drug development were with companies that had no approved product on the U.S. market.

Weighing Benefit and Risk

It should be noted that FDA assesses the benefit-risk of new drugs on a case-by-case basis, considering the degree of unmet medical need and the severity and morbidity of the condition the drug is intended to treat. This approach has been critical to increasing patient access to new drugs for cancer and rare and other serious diseases, where existing therapies have been few and limited in their effectiveness. Some of these products have serious side effects but they were approved because the benefit outweighed the risk. For example, in March of last year, FDA approved Yervoy (ipilimumab) for the treatment of unresectable or metastatic melanoma. Yervoy also poses a risk of serious side effects in 12.9 percent of patients treated, including severe to fatal autoimmune reactions. However, FDA decided that the benefits of Yervoy outweighed its risks, especially considering that no other melanoma treatment has been shown to prolong a patient's life.

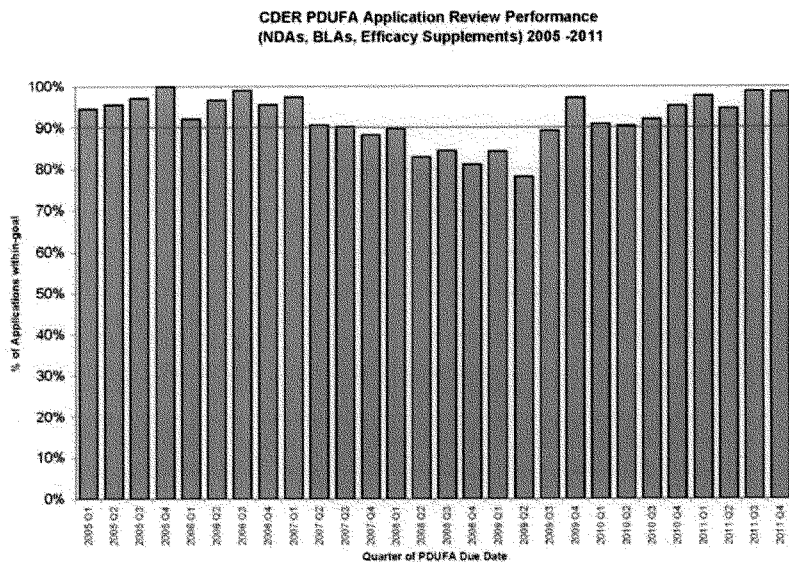
As discussed in more detail below, PDUFA V will enable FDA to develop an enhanced, structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency's drug regulatory decision-making.

Challenges for the Current Drug Program

Although we can report many important successes with the current program, new challenges have also emerged that offer an opportunity for further enhancement. While new authorities from the Food and Drug Administration Amendments Act of 2007 (FDAAA) have strengthened drug safety, they have put strains on FDA's ability to meet premarket review performance goals and address post-market review activities. In addition, there has been a significant increase in the number of foreign sites included in clinical trials to test drug safety and effectiveness, and an increase in the number of foreign facilities used in manufacturing new drugs for the U.S. market. While foreign sites can play an important role in enabling access to

new drugs, the need to travel much farther to conduct pre-approval inspections for clinical trials and manufacturing sites overseas has created additional challenges for completion of FDA's review within the existing PDUFA review performance goals, while at the same time trying to communicate with sponsors to see if identified issues can be resolved before the review performance goal date.

Despite these challenges, FDA has maintained strong performance in meeting the PDUFA application review goals, with the exception of a dip in FY 2008-09, when staff resources were shifted within the discretion afforded FDA to ensure timely implementation of all the new FDAAA provisions that affected activities in the new drug review process. Recent performance data show that FDA has returned to meeting or exceeding goals for review of marketing applications under PDUFA. This is shown in Figure 3.



CDER data as of 12/31/2011. Figures reflect aggregate performance for all NDAs, BLAs, and Efficacy Supplements based on the month of the PDUFA review goal.

However, FDA wants to meet not only the letter, but also the spirit of the PDUFA program. That is, we want to speed patient access to drugs shown to be safe and effective for the indicated uses while also meeting our PDUFA goals.

The NDA/BLA approval phase of drug development is reported to have the highest success rate of any phase of drug development. That is, the percentage of drugs that fail after the sponsor submits an NDA/BLA to FDA is less than the percentages that fail in preclinical development and in each phase of clinical development. At the same time, it is critical to our public health mission that we work with industry and other stakeholders to take steps to reduce uncertainty and increase the success of all phases of drug development. We must leverage advances in science and technology to make sure that we have the knowledge and tools we need

to rapidly and meaningfully evaluate medical products. The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products—known as regulatory science—is about more than just speeding drug development prior to the point at which FDA receives an application for review and approval. It also gives us the scientific tools to modernize and streamline our regulatory process. With so much at stake for public health, FDA has made advances in regulatory science a top priority. The Agency is both supporting mission-critical science at FDA and exploring a range of new partnerships with the National Institutes of Health (NIH) and academic institutions to develop the science needed to maximize advances in biomedical research and bring the development and assessment of promising new therapies and devices into the 21st century. With this effort, FDA is poised to support a wave of innovation to transform medicine and save lives.

For example, FDA is working to improve the science behind certain clinical trial designs. Recent advances in two clinical trial designs—called non-inferiority and adaptive designs—have required FDA to conduct more complex reviews of clinical trial protocols and new marketing applications. Improving the scientific bases of these trial designs should add efficiency to the drug review process, encourage the development of novel products, and speed new therapies to patients.

FDA also has taken steps to help facilitate the development and approval of safe and effective drugs for Americans with rare diseases. 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.

PDUFA Reauthorization

In PDUFA IV, Congress directed FDA to take additional steps to ensure that public stakeholders, including consumer, patient, and health care professional organizations, would have adequate opportunity to provide input to the reauthorization and any program enhancements for PDUFA V. Congress directed the Agency to hold an initial public meeting and then to meet with public stakeholders periodically, while conducting negotiations with industry to hear their views on the reauthorization and their suggestions for changes to the PDUFA performance goals. PDUFA IV also required that minutes from negotiation sessions held with industry be made public.

Based on a public meeting held in April 2010, input from a public docket, and the Agency's own internal analyses of program challenge areas, FDA developed a set of potential proposed enhancements for PDUFA V and in July 2010, began negotiations with industry and parallel discussions with public stakeholders. These discussions concluded in May 2011 and we held a public meeting on October 24, 2011, where we solicited comments on the proposed recommendations. We also opened a public docket for comments. We considered these comments, and on January 13, 2012, we transmitted the final recommendations to Congress.

We are very pleased to report that the enhancements for PDUFA V address many of the top priorities identified by public stakeholders, the top concerns identified by industry, and the most important challenges identified within FDA. PDUFA V enhancements include a review program for New Drug Applications, New Molecular Entities, and Original Biologics License Applications, regulatory science enhancements to expedite drug development, risk-benefit assessment enhancements, FDA drug safety system enhancement and modernization, requiring electronic submissions and standardization of electronic application data, a user fee increase, and enhancements for a modified inflation adjuster and additional evaluations of the workload adjuster.

Generic Drug User Fees

As a result of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as Hatch-Waxman Amendments passed by Congress more than a quarter of a century ago, America's generic drug industry has been developing, manufacturing, and marketing—and FDA has been reviewing and approving—lower-cost versions of brand-name drugs. This legislation and the industry it fostered has been a true public health success. Last year, approximately 78 percent of the more than 3 billion new and refilled prescriptions dispensed in the United States were filled with generics. In the last decade alone, generic drugs have provided more than \$931 billion in savings to the nation's health care system.⁵

This success, however, also has come to represent a significant regulatory challenge, and delays in approvals of generic drugs have emerged as a major concern for the generics industry, FDA, consumers, and payers alike. Unlike the brand manufacturers who pay fees under PDUFA, the generic industry does not pay a user fee to support FDA activities related to its

⁵ "An Economic Analysis of Generic Drug Usage in the U.S." Independent Analysis by IMS Health, Sept. 2011, <http://gphaonline.org/sites/default/files/GPhA%20IMS%20Study%20WEB%20Sep20%2011.pdf>.

applications. Over the last several years, the time it takes for FDA to approve a generic drug has nearly doubled as FDA's resources have not kept pace with an increasing number of Abbreviated New Drug Applications (ANDA) and other submissions related to generic drugs. The number of generic drug submissions sent annually to FDA has grown rapidly, reaching another record high this year, including nearly 1,000 ANDAs. Drug Master Files⁶ have grown at a comparable pace and have reached similar heights. The current backlog of applications pending review is estimated to be over 2,500. The current median time to approval is approximately 31 months, though it should be noted that this includes time the application is back with the sponsor to answer any questions FDA may have about the application.

The regulatory challenge of ensuring safe, high-quality generic drugs includes inspecting manufacturing facilities, where the challenge is not just one of numbers but also of geography. To keep pace with the growth of the generic drug industry, FDA has had to conduct more inspections as the number of facilities supporting those applications has also increased, with the greatest increase coming from foreign facilities. Currently, the number of foreign Finished Dosage Form (FDF)⁷ manufacturers exceeds the number found in the United States. The generic industry is also experiencing significant growth in India and China, a trend expected to continue. Foreign inspections represent a significant challenge and require significant resources.

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

⁶ Drug Master Files are widely used to provide FDA with information about the drug substance, also known as the active pharmaceutical ingredient (API).

⁷ An FDF is the final drug product (e.g. tablet, capsule). An FDF is made up of both API(s) and any inactive excipients.

Overview of the Proposed Generic Drug User Fee Program

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

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

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

potential to dramatically reduce the time needed to commercialize a generic drug, when compared to pre-GDUFA review times.

In addition, the variety of funding sources for the program will ensure that participants in the generic drug industry, whether FDF manufacturers or API⁸ manufacturers, whether foreign or domestic, appropriately share the financial expense and benefits of the program. The broad range of funding sources, including and across facility and application types, as well as the large number of each, ensures that individual fees remain reasonable and significantly lower than associated branded drug fees.

As in all of FDA's other medical product user fee programs, under the proposed generic drug user fee program, user fee funding would supplement appropriated funding to ensure sufficient resources for the Agency's generic drug review program, and guarantees are in place to ensure that the user fees are supplemental to annual appropriations in the budget.

Biosimilars User Fees

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

⁸ An API is the drug substance responsible for the therapeutic effect (e.g. the chemical aspirin that is combined with excipients to produce the FDF aspirin tablet).

reference product. This program will provide significant benefits for patients, making available more affordable treatments that clinicians will know are biosimilar or interchangeable. The development of this new market segment will expand the opportunities for technical innovation and job growth.

Background

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

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

Program Funding and Metrics

The proposed biosimilars user fee program for FY 2013 to 2017 addresses many of the top priorities identified by public and industry stakeholders and the most important

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

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

The biosimilars user fee program would support FDA activities at the application stage, such as review of advertising and labeling prior to approval of a biosimilar biological product application or supplement; review of required post-marketing studies and post-marketing studies that have been agreed to by sponsors as a condition of approval; the issuance of action letters that communicate decisions on biosimilar biological product applications; and inspection of biosimilar biological product establishments and other facilities undertaken as part of FDA's

review of pending biosimilar biological product applications and supplements (but not inspections unrelated to the review of biosimilar biological product applications and supplements). Finally, it would support some activities at the post-approval stage, such as post-marketing safety activities, with respect to biologics approved under biosimilar biological product applications or supplements.

Best Pharmaceuticals for Children Act /Pediatric Research Equity Act

Background

The Best Pharmaceuticals for Children Act (BPCA), enacted in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA) and reauthorized in 2002 and 2007, provides incentives to manufacturers who voluntarily conduct studies of drugs in children. This law provides six months of additional exclusivity for a drug (active moiety), in return for conducting pediatric studies in response to a written request (WR) issued by FDA. To qualify for pediatric exclusivity, the pediatric studies must “fairly respond” to a WR issued by FDA that describes the needed pediatric studies (including, for example, indications to be studied or number of patients). The Patient Protection and Affordable Care Act (Affordable Care Act) extended availability of pediatric exclusivity to biological products but, due to the recent nature of this change, no biological product has received pediatric exclusivity to date.

The Pediatric Research Equity Act (PREA), enacted in 2003, works in concert with BPCA. PREA provides FDA the authority to require pediatric studies under certain conditions. PREA requires pediatric assessments of drugs and biological products for the same indications previously approved or pending approval, when the sponsor submits an application or supplemental application to FDA for a new indication, new dosing regimen, new active ingredient, new dosage form, or new route of administration.

Both BPCA and PREA expire September 30, 2012, if not reauthorized.

Need for Pediatric Information

Before enactment of BPCA in 1997, approximately 80 percent of medication labels in the Physician's Desk Reference did not have pediatric-use information—data to establish the correct dose for pediatric patients or confirm safety or efficacy in the pediatric population. All too often health care professionals were forced to rely on imprecise and ineffective methods to provide medications for children, such as adjusting dosing based on weight or crushing pills and mixing them in food. Pediatric patients are subject to many of the same diseases as adults and are, by necessity, often treated with the same drugs and biological products as adults. Inadequate dosing information may expose pediatric patients to overdosing or underdosing. Overdosing may increase the risk of adverse reactions that could be avoided with an appropriate pediatric dose; underdosing may lead to ineffective treatment. The lack of pediatric-specific safety information in product labeling also means caretakers and health care professionals are unable to monitor for and manage pediatric-specific adverse events. In situations where younger pediatric populations cannot take the adult formulation of a product, the failure to develop a pediatric formulation that can be used by young children (e.g., a liquid or chewable tablet) also can deny children access to important medications.

Success of BPCA and PREA

Together, BPCA and PREA have generated pediatric studies on many drugs and helped to provide important new safety, effectiveness, and dosing information for drugs used in

children. Both statutes continue to foster an environment that promotes pediatric studies and to build an infrastructure for pediatric trials that was previously non-existent.

Over the past 15 years, approximately 400 drugs have been studied and labeled for pediatric use under these two laws. Since 1997, BPCA, the exclusivity incentive program, has generated labeling changes for 250 products. The labeling for 120 products has been updated to include new information, expanding use of the product to a broader pediatric population; the labeling of 29 products had specific dosing adjustments; the labeling of 69 products was changed to show that the products were found not to be safe and effective for children; and 55 products had new or enhanced pediatric safety information added to the labeling.⁹

Since PREA was enacted, FDA has approved approximately 1,450 NDAs and supplemental NDAs that fell within the scope of PREA (i.e., applications for new active ingredients, new dosage forms, new indications, new routes of administration, or new dosing regimens). These approvals have resulted in approximately 231 labeling changes involving pediatric studies linked to PREA assessments. In addition, FDA has approved approximately 105 BLAs and supplemental BLAs that fell within the scope of PREA.

Examples of New Pediatric Information Generated by BPCA and PREA

- Migraine headaches – Axert (almotriptan) was studied and labeled for age 12 years and older. Before enactment of BPCA and PREA, no medications were studied and labeled for migraines in children.

⁹ These numbers add up to a number greater than 205 because some products had more than one change to the labeling.

- Diabetes – Apidra (insulin glulisine recombinant) has been studied and labeled down to age 4 for Type 1 diabetes.
- Arthritis – Actemra (tocilizumab) has been studied and labeled down to age 2 for Active Systemic Juvenile Idiopathic Arthritis (SJIA).
- Pain – Ofirmev/acetaminophen injection has been studied and labeled down to age 2 for mild-to-moderate pain/moderate-to-severe pain with adjunctive opioid analgesics and reduction of fever.
- Brain Tumors – Afinitor (everolimus) has been studied and labeled down to age 3 for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

BPCA and PREA require review of adverse event reports on a regular basis. To date, adverse event reviews have been presented to the Pediatric Advisory Committee (PAC) for 129 products. In addition, as directed by BPCA, FDA has worked with NIH and the Foundation for the National Institutes of Health (FNIH) to facilitate the study of off-patent drugs not eligible for exclusivity under BPCA.

Despite the successes of these two programs, there is more work to be done. There is still a large number of drug and biological products that are inadequately labeled for children. More broadly, long-term safety and effects on growth, learning, and behavior are critically important to the safe use of certain medications and continue to be understudied. Due to technical challenges and the need for sequential studies, slow but deliberate progress is being made studying the safety and efficacy of approved therapies used to treat neonates (age birth to one month). These issues are still of concern, as it is this youngest population that is undergoing marked physiologic and developmental changes, which are affected by drug therapies.

FDA welcomes the opportunity to work with Congress to ensure that the benefits of an incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs.

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.

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.

Drug Shortages

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

control, we are committed to addressing this important issue and look forward to working with this Subcommittee on this issue.

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

When FDA learns of a potential shortage situation, we work directly with the affected manufacturer to help prevent the shortage or to minimize its effect on patients. This may include developing temporary workaround solutions to manufacturing or quality issues; consulting with the manufacturer to resolve the underlying problem; or helping the manufacturer find additional sources of raw materials. We also expedite the review of submissions by the manufacturer that may alleviate the drug shortage while continuing to meet safety standards, which may include requests to extend the expiration date of products, make manufacturing changes to increase capacity, use a new raw material source, or change product specifications. FDA can also use our regulatory discretion for a manufacturer to continue marketing a medically necessary drug, if the manufacturer can develop a method to resolve a quality issue prior to the drug's administration. A recent example was potassium phosphate, which is a medically necessary injectable drug needed for intravenous nutrition in critically ill patients. The firm found glass particles in the vials, posing a significant safety concern. The manufacturer was able to provide data to FDA showing the particles could successfully be removed with a filter. FDA then exercised enforcement discretion for the drug to be shipped with a letter to notify health care professionals

that the filter needed to be used with the drug. This resulted in the drug being available for patients in a safe manner while the firm addressed the particulate issue for future production.

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

For example, FDA announced on February 21, 2012, that in response to the critical shortage of the cancer drug Doxil (doxorubicin hydrochloride liposome injection) and rapidly declining supplies of methotrexate, FDA took proactive steps needed to increase available supply for patients in the United States. For Doxil, FDA exercised enforcement discretion to allow temporary importation of a replacement drug, Lipodox (doxorubicin hydrochloride liposome injection). With regard to methotrexate, FDA successfully engaged many firms to assist in maintaining supplies to meet all patient needs, in addition to approving a preservative-free methotrexate generic application, which we prioritized.

Although our work has enabled the Agency to successfully prevent 255 potential shortages since the beginning of 2010, drug shortages are on the rise. In response to this growing problem, the Administration has taken several actions to better understand and respond to drug shortages. On September 26, 2011, FDA hosted a public meeting to gain additional insight into the causes and impacts of drug shortages and possible strategies for preventing or mitigating drug shortages. Interested parties who attended included professional societies,

patient advocates, industry, researchers, pharmacists, and other health care professionals. A docket has been opened in relation to the public workshop, where comments can be received from the public.

On October 31, 2011, the President issued an Executive Order,¹⁰ which directed FDA, as well as the Department of Justice, to take action to help further reduce and prevent drug shortages, protect consumers, and prevent inappropriate stockpiling and exorbitant pricing of prescription drugs in shortage situations. In an effort to encourage broader reporting of manufacturing discontinuances, the President's order directs FDA to use all appropriate administrative tools to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life-supporting or life-sustaining, or that prevent debilitating disease. The Executive Order also requires FDA to expand its current efforts to expedite review of new manufacturing sites, drug suppliers, and manufacturing changes to help prevent shortages. Under the President's Order, FDA is also directed to report to the Department of Justice situations in which secondary wholesalers or other market participants have responded to potential drug shortages by stockpiling medications or pricing drugs exorbitantly, so that the Department of Justice can determine whether these actions are consistent with applicable law. Since the issuance of the Executive Order, FDA has successfully prevented 118 drug shortages.

On the same day the President signed the Executive Order, the Administration announced its support for bipartisan bills (S. 296 and H.R. 2245) that would require all prescription drug shortages to be reported to FDA and would give FDA new authority to enforce these requirements. The Administration also announced that FDA would provide additional staffing resources to enhance the Agency's ability to prevent and mitigate drug shortages. Additionally,

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

FDA released a report entitled “A Review of FDA’s Approach to Medical Product Shortages” on its role in monitoring, preventing, and mitigating drug shortages, which included recommendations to further reduce the impact of these shortages.

In addition, FDA sent a letter to pharmaceutical manufacturers, reminding them of their current legal obligations to report certain discontinuances to the Agency, and urging them to voluntarily notify FDA of all potential disruptions of the prescription drug supply to the U.S. market, even where disclosure is not currently required by law. The letters to manufacturers and the Executive Order have produced a significant increase in the number of potential shortages reported to FDA. In the 10 months preceding the Administration’s actions (January through October 2011), the Agency received an average of approximately 10 notifications per month. In the four weeks following the letters to the manufacturers and issuance of the Executive Order, we received 61 notifications, a six-fold increase. This increased level of reporting by manufacturers of potential supply problems has continued into 2012.

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

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

- Doubling the number of staff in the Center to assist in coordination and response activities, as well as expediting actions (e.g., inspections) that would help to alleviate drug shortages;
- Meeting with various stakeholders to discuss shared opportunities to prevent and mitigate shortages, including the Generic Pharmaceutical Association, the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization, manufacturers, and wholesalers;
- Exploring options for improving our drug shortage database for the tracking of shortages, as well as utilizing the database to develop prediction models for drug shortages;
- Working with the Department of Justice, as directed in the Executive Order, regarding issues related to stockpiling and exorbitant pricing, including reports from pharmacists and other health care professionals in connection with drug shortages; and
- Continuing to prioritize review applications for products that are in shortage situations.

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

CONCLUSION

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.

Dr. Shuren, you are recognized for 5 minutes for your opening statement.

STATEMENT OF JEFFREY SHUREN

Dr. SHUREN. Mr. Chairman and members of the committee, thank you for the opportunity to testify today.

As you know, on February 15th, FDA and representatives from the medical device industry reached an agreement on proposed recommendations for the reauthorization of the Medical Device User Fee Act, or MDUFA, the details of which we provided to you on March 16th. As required by law, we held a public meeting on March 28th and sought public comment on the proposal package. We plan to send the final package to you by the end of this week.

When I came to CDRH in 2009, in response to concerns expressed by industry and others, we initiated a review of our device premarket review programs. The following year, we released two reports that concluded as I have testified before that we had not done as good a job managing the review programs as we should have. The number one problem we found was insufficient predictability, which was leading to inefficiencies, higher costs for industry and FDA, sometimes delays in bringing safe and effective products to market.

In January 2011, we announced a plan with 25 specific actions that we would take that year to improve the predictability, consistency and transparency of our premarket programs. We announced additional steps since then. As of today, 30 actions have been completed or well underway. They are intended to create a culture change toward greater collaboration, interaction, transparency and the appropriate balancing of benefits and risk. They focused on assuring predictable and consistent decision making and application of the least-burdensome principle and implementing more efficient regulatory processes.

Preliminary data indicate that the actions we have taken have started to bear fruit. For example, the backlog of 510(k) submissions that had been steadily increasing from 2005 to 2010 decreased for the first time last year and are continuing to decline in 2012. The backlog of PMA submissions that had been steadily increasing from 2007 to 2011 has decreased this year for the first time, and average total time for review appears to be decreasing for the first time as well.

However, we still have much work to do. Reauthorization of MDUFA will provide the resources that CDRH needs to continue improving the device review programs and help reduce the high staff turnover that has adversely affected review predictability and consistency. The proposed MDUFA recommendations we have agreed upon with industry includes several important process improvements. For example, if a performance goal on a device application is missed, the MDUFA proposal would require FDA and applicants to work out a plan to complete the work on the submission, ensuring that no submission would be left behind, and requiring a new substantive interaction between FDA and an applicant would help assure sufficient time for the applicant to properly respond to appropriate questions. These and other proposed enhance-

ments are intended to achieve a shared outcome goal of reduced average total time to decision, which both we and industry believe is an important indicator of a successful premarket review program.

The agreement we have reached with industry strikes a careful balance between what industry agreed to pay and what FDA can accomplish with the amount of funding proposed. However, we have concern that even if device user fee resources are increased under MDUFA III, additional new legislative mandates imposed on CDRH could divert resources and undermine FDA's ability to achieve the new performance goals. We are very willing to work with Congress on initiatives that complement the user fee agreement. However, just as FDA and industry mutually agreed that some initiatives would be part of the formal agreement, we also agree that some initiatives would not be part of the agreement. Additional legislation to codify initiatives the agency and industry chose not to devote resources to risks diverting resources from achieving MDUFA goals and could undermine the user fee agreement entirely.

When PDUFA was last reauthorized in 2007, as you heard, the addition of new policy-related requirements ultimately resulted in FDA's drug review program having to temporarily suspend meeting its PDUFA review goals in order to meet the statutory mandates. We want to avoid such a situation so that CDRH can focus on meeting the ambitious new proposed MDUFA program goals and achieving timely patient access to safe and effective devices, which is an objective that we share with industry, health care practitioners, patients, consumers and you.

Mr. Chairman, we share your goal of timely reauthorization of MDUFA. We look forward to working with you toward enactment of this critical legislation. I commend the subcommittee's efforts and am pleased to answer any questions the subcommittee may have. Thank you.

[The prepared statement of Dr. Shuren follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

**STATEMENT
OF
JEFFREY SHUREN, M.D., J.D.
DIRECTOR
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH**

**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: HOW INNOVATION HELPS PATIENTS AND JOBS"

April 18, 2012

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss reauthorization of the Medical Device User Fee Act, or MDUFA.

Background on MDUFA

The enactment in 2002 of the Medical Device User Fee and Modernization Act (MDUFMA I) was prompted by growing concerns about the medical device review program's capacity and performance. MDUFMA I and MDUFA II (enacted in 2007) authorized user fees for the review of medical device premarket applications, reports, supplements, and premarket notification submissions. These additional resources enabled FDA to make its reviews more timely, predictable, and transparent to applicants. MDUFA fees and mandated appropriations for the medical device program helped FDA expand available expertise, modernize its information management systems, provide new review options, and provide more guidance to prospective applicants.

MDUFA authorizes FDA to collect user fees for certain medical device applications, the registration of certain medical device establishments, and certain other purposes. Small businesses may qualify for a waiver or a reduced fee on certain submissions to FDA.

Of the total \$292,707,540 obligated in support of the process for the review of medical device submissions in FY 2010, MDUFA fees funded about 20 percent. The remainder of the funding was through appropriations. Fees currently charged for device review under MDUFA include \$220,050 for a Premarket Approval (PMA) application for high-risk medical devices (a

business with gross receipts under \$100 million qualifies for the “small business” PMA fee of about \$55,000, and for firms with gross receipts under \$30 million, the firm’s first PMA fee is also waived). For lower-risk devices cleared under the 510(k) review program, manufacturers pay \$4,049 per 510(k) application review (\$2,024 for small businesses).¹ As a point of comparison, PDUFA fees—nearly \$568 million in FY 2010—currently account for about two-thirds of the drug review program’s budget, and the current fee for FY 2012 associated with review of a New Drug Application (NDA) requiring clinical data is \$1,841,500.²

The medical device user fee program has produced benefits for public health. A better-resourced premarket device review program has enhanced FDA’s abilities to help bring more safe and effective medical devices to the market, while keeping pace with the increasing complexity of technology and changes in clinical practice. Since MDUFA II was reauthorized in 2007, FDA has approved 106 original PMAs and cleared more than 13,000 devices under the 510(k) program.

For example, approvals have included devices intended to address unmet needs in the pediatric population, such as the first heart pump designed to support the hearts of infants to adolescents until they receive a heart transplant, and the first percutaneous heart valve (approved for both children and adults).

The device program also has approved important new laboratory tests, including an emergency-use diagnostic test in response to H1N1 outbreak in humans, and the first quick test for malaria. Device reviews have significantly contributed to the very important trend toward

¹ See U.S. FDA, “Medical Device User Fee Rates for Fiscal Year 2012,” 76 *Federal Register* 45,826-45,831 (Aug. 1, 2011), available at <http://www.gpo.gov/fdsys/pkg/FR-2011-08-01/html/2011-19335.htm>.

² See U.S. FDA, “Prescription Drug User Fee Rates for Fiscal Year 2012,” 76 *Federal Register* 45,831-45,838 (Aug. 1, 2011), available at <http://www.gpo.gov/fdsys/pkg/FR-2011-08-01/pdf/2011-19332.pdf>.

personalized medicine through clearance of a test system that can assist in assessing the risk of tumor recurrence and long-term survival for patients with relatively high-risk breast cancer.

Other important devices that have become available to patients over the course of MDUFA II include, for example, the Implantable Miniature Telescope (IMT), used for monocular implantation to improve vision in elderly patients with stable severe to profound vision impairment associated with end-stage age-related macular degeneration (AMD)³; the Infrascanner™ infrared brain hematoma detector, a non-invasive hand-held device that uses near-infrared spectroscopy to evaluate suspected brain hematomas at the site of injury within the “golden hour” (the period following head trauma when pre-hospital analysis is needed to rapidly assess a patient’s neurological condition)⁴; and the NeuRx DPS™ RA/4 Respiratory Stimulation System, an implantable electronic device that stimulates the diaphragm and allows certain spinal cord injury patients to breathe for at least four hours a day without a mechanical ventilator.⁵

However, neither the FDA nor industry believe that the user fee program has reached the level of performance, or produced the extent of benefits, that it has the potential to achieve.

MDUFA II Performance

FDA has been meeting or exceeding goals agreed to by FDA and industry under MDUFA II for approximately 95 percent of the submissions we review each year. For example, FDA completes at least 90 percent of 510(k) reviews within 90 days or less. In the few areas where FDA is not yet meeting its MDUFA goals, the Agency’s performance has generally been

³ See FDA News Release, “FDA Approves First Implantable Miniature Telescope to Improve Sight of AMD Patients” (July 6, 2010), available at

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm218066.htm>.

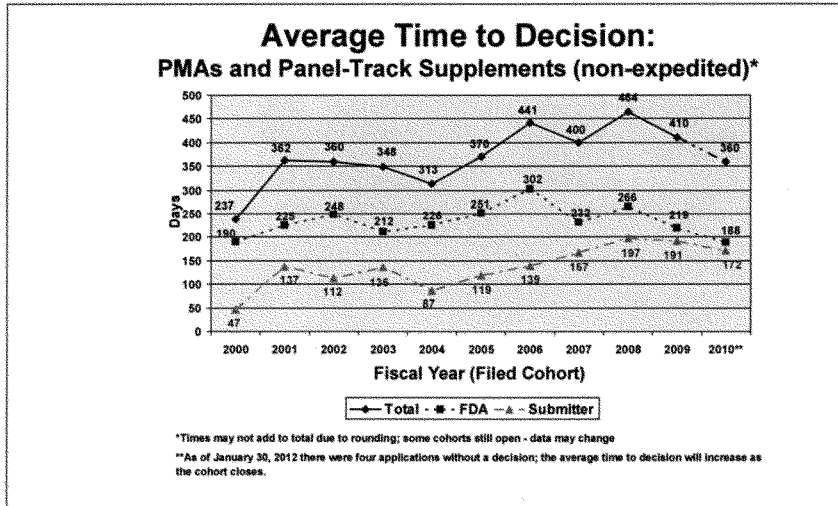
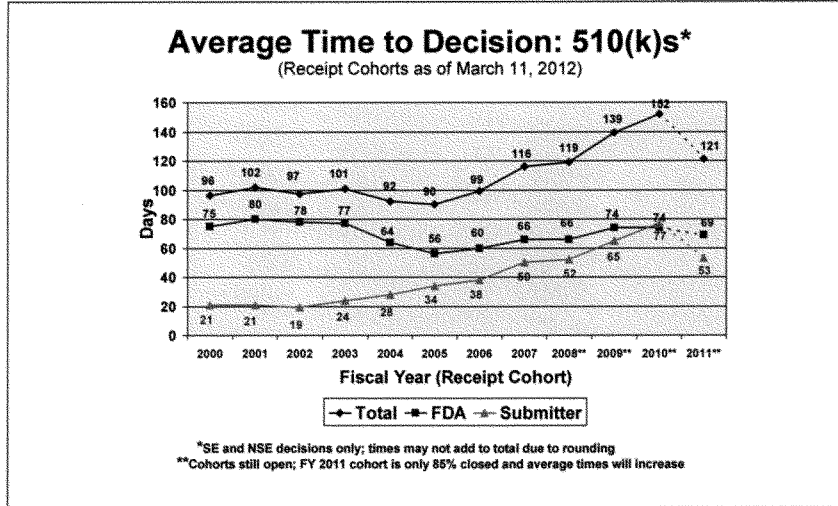
⁴ See Office of Naval Research, “Naval Technology Could be a Lifesaver” (Dec. 21, 2011), available at <http://www.onr.navy.mil/Media-Center/Press-Releases/2011/Infrascanner-brain-TBI-FDA-approval.aspx>.

⁵ See FDA News Release, “FDA Approves Diaphragm-Pacing Device” (June 18, 2008), available at <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm116914.htm>.

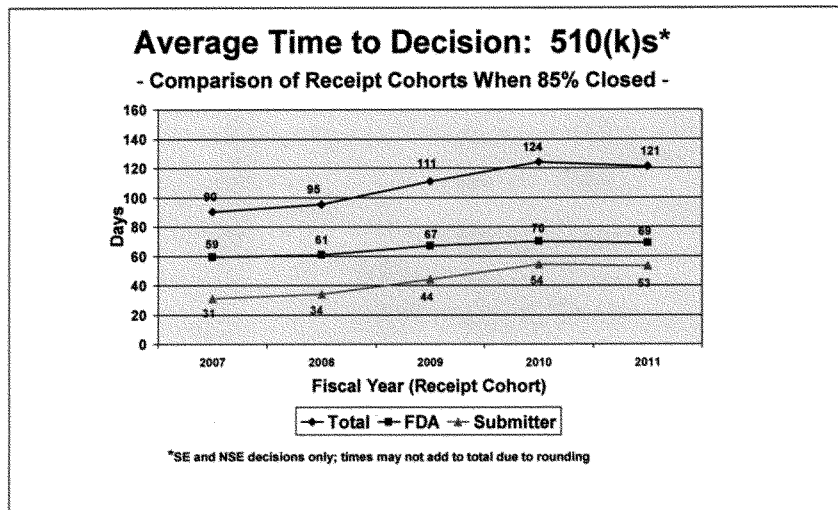
improving—despite growing device complexity and an increased workload. FDA’s performance over the course of MDUFA II has not been limited to achieving quantitative goals for the timely review of premarket submissions like PMAs and 510(k)s; we have also accomplished a number of “qualitative” goals set by MDUFA II in 2007, including issuing more than 50 new and updated guidances for industry. Guidance documents are important resources for industry because they describe the Agency’s interpretation of, or policy on, regulatory issues, and as such, are critical to support industry efforts to comply with the law and develop new products that may benefit the public health.⁶ The availability of guidance documents also facilitates regulatory predictability and consistency.

It is important to note that MDUFA metrics reflect FDA time only; they do not reflect the time taken by device sponsors to respond to requests for additional information. *Overall* time to decision—the time that FDA has the application, *plus* the time the manufacturer spends answering any questions FDA may have—has increased steadily since 2001. As the graphs below illustrate, while the time FDA spends reviewing an application has improved (for both low- and high-risk devices), average total days for the review of 510(k)s has been increasing since 2005, and has been increasing for PMA applications since 2004.

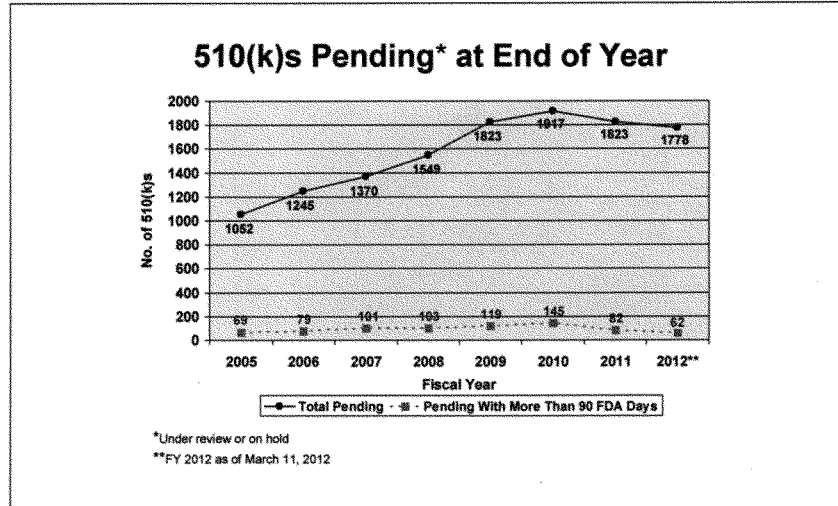
⁶ Guidance documents include documents that relate to: (1) the design, production, labeling, promotion, manufacturing, and testing of regulated products; (2) the processing, content, and evaluation or approval of submissions; and (3) FDA’s inspection and enforcement policies. See generally, “Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency” (issued Dec. 2011), available at <http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM285124.pdf>.



FDA bears some responsibility for the increase in total time to decision, and we have been instituting management, policy, and process changes to address this issue. As a result, we are starting to see indicators of improved review performance. For example, the Agency has currently completed review of 85 percent of the 510(k) submissions received in FY 2011. The graph below, illustrating average time to decision during the last five years at this same point (85 percent of 510(k)s reviewed), shows that progress was made, starting last year, in stabilizing 510(k) review times.

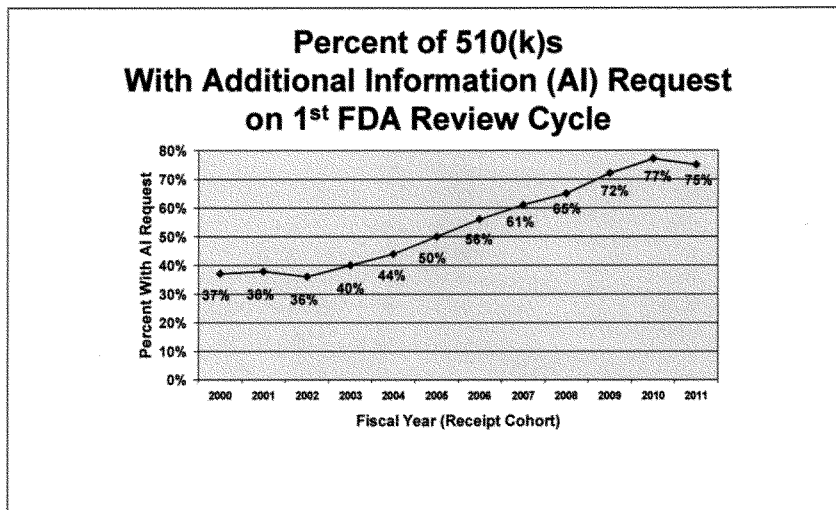


In addition, in FY 2011, CDRH for the first time began reducing what previously was an increasing backlog of unresolved 510(k) submissions, as indicated in the chart below—and that trend is clearly continuing as we approach the mid-point of FY 2012:



Likewise, there had been a continuous annual increase, since FY 2002, in the percentage of 510(k) submissions requiring an Additional Information (AI) letter⁷ after the first review cycle, which had contributed to the increasing total time from submission to decision. As indicated in the chart below, however, in FY 2011, the percentage of 510(k)s requiring an AI letter declined for the first time since 2002.

⁷ If, after reviewing an application, FDA determines that it cannot approve or clear the application in its current form, FDA sends a letter informing the sponsor of this decision. For 510(k) applications, this is called an "Additional Information" (AI) letter.



Smart Regulation's Role in Facilitating Medical Device Innovation

FDA recognizes that, if the United States is to maintain its leadership role in this area, we must continue to streamline and modernize our processes and procedures to make device approval not just scientifically rigorous, but clear, consistent, and predictable, without compromising safety. We are committed to continued improvements in the device approval process to address legitimate concerns raised by industry and other stakeholders.

A little over two years ago, CDRH recognized that, given the growing complexities of medical product development, we needed to re-evaluate and modernize our regulatory review processes in order to ensure that patients had timely access to safe and effective medical devices. At that time, CDRH began to undertake a new systematic approach to device regulation, moving away from the traditional misperception that safety and effectiveness and innovation are

incompatible. Rather than focus on *more* regulation or *less* regulation, we began to focus on “smart regulation.”

Our goal has been to ensure that safety and effectiveness and innovation are complementary, mutually supporting aspects of our mission to promote the public health. As part of our process to improve CDRH’s internal systems, we first reached out to stakeholders to hear their concerns and listen to their recommendations about our premarket programs. This is what we heard: industry felt that inadequate predictability, consistency, and transparency were stifling innovation and driving jobs overseas; and consumer groups, third-party payers, and some health care professionals believed that one of our premarket pathways—the 510(k) program—did not provide adequate protection for American patients and did not generate sufficient information for practitioners and patients to make well-informed treatment and diagnostic decisions. In turn, CDRH employees expressed concerns that the 510(k) program had not adapted to the increasing complexity of devices, and that poor-quality 510(k) submissions, poor-quality clinical studies conducted in support of PMA applications, and an ever-growing workload were straining already overburdened premarket programs.

We also began two assessments of our premarket programs to identify issues, their root causes, and the appropriate solutions. One assessment focuses on the 510(k) program. The other looks at how we use science in regulatory decision-making, touching on aspects of several of our premarket review pathways, such as our clinical trials program. In addition, we contracted with the Institute of Medicine (IOM) to conduct an independent evaluation of our 510(k) program.

In August 2010, following extensive public input, we released two reports that identified issues regarding our premarket programs and proposed potential actions for us to take to address the underlying root causes. The number one problem we found was insufficient predictability in

our premarket programs, which can create inefficiencies, increase costs for industry and FDA, and delay bringing safe and effective products to market. We identified several root causes of these issues. They include very high reviewer and manager turnover at CDRH (almost double that of FDA's drug and biologics centers); insufficient training for staff and industry; extremely high ratios of employees to front-line supervisors; insufficient oversight by managers; CDRH's rapidly growing workload, caused by the increasing complexity of devices and the number of overall submissions we review; unnecessary and/or inconsistent data requirements imposed on device sponsors; insufficient guidance for industry and FDA staff; and poor-quality submissions from industry.

While it is true that providing more user fee resources alone won't solve the problems with our premarket programs, insufficient funding is at the root of, or a contributing factor to, several of these problems. Adequate and stable funding is one key component to our and industry's success in bringing safe and effective devices to market quickly and efficiently.

After considering extensive and varied public input on our recommendations, in January 2011, FDA announced a Plan of Action that included 25 specific actions that we would take in 2011 to improve the predictability, consistency, and transparency of our premarket programs. We continued to engage in dialogue about issues of importance to CDRH and to members of the public, including the medical device industry, health care professionals, patients, and

consumers,⁸ and followed up the Plan of Action with eight additional steps we would take. As of April 2012, 29 actions are already completed or are well underway.⁹

In February 2011, we announced our Innovation Initiative, which included several proposals to help maintain the position of the United States as the world's leader in medical device innovation, including the creation of a new approach for important, new technologies called the Innovation Pathway. On April 9, 2012, CDRH launched its second version of the Innovation Pathway, called "Innovation Pathway 2.0." Innovation Pathway 2.0 offers new and modified tools and methods to deepen collaboration between FDA and innovators early in the process, prior to premarket submission, with the goal of making the regulatory process more efficient and timely. The Pathway also serves as a living laboratory to test new tools and methods for breakthrough devices that we may also apply to other technologies to enhance all of our device premarket programs. Under the Pathway, CDRH selected three companies with promising breakthrough treatments for end-stage renal disease (ESRD), which is an area of growing public health concern that could benefit from innovative technology. We plan to accept up to five more companies during the year with promising, breakthrough treatments for ESRD to participate in the Innovation Pathway and to test out new tools for reducing the time and cost of device development and assessment.

We have announced additional efforts to improve our premarket programs, including actions to improve our program for clinical trials and the Investigational Device Exemption

⁸ Numerous public meetings and workshops, including three "town hall" discussions with the Center Director and senior CDRH management, were held in 2011; similar CDRH outreach to stakeholders is ongoing. For more details, see <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm111051.htm>.

⁹ More information about FDA's progress in implementing the CDRH "Plan of Action for 510(k) and Science" is available on FDA's website at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm276286.htm>.

(IDE) program. The actions we are taking can be grouped into three main areas of emphasis.

Overall, our actions seek to:

- Create a culture change toward greater transparency, interaction, collaboration, and the appropriate balancing of benefits and risks;
- Ensure more predictable and consistent recommendations, decision-making, and application of the least-burdensome principle; and
- Implement more efficient processes and use of resources.

Specific steps that we are taking include:

- Issuing guidance clarifying the criteria used to make benefit-risk determinations a part of device premarket decisions. This will provide greater predictability and consistency and apply a more patient-centric approach by considering patients' tolerance for risk in appropriate cases (draft guidance issued August 15, 2011, and final guidance issued on March 27, 2012);
- Creating standard operating procedures for when a reviewer can request additional information regarding a premarket submission and identifying at what management level the decision must be made. These steps are intended to provide greater predictability, consistency, and the appropriate application of the least-burdensome principle by reducing the number of inappropriate information requests (Standard Operating Procedures issued November 10, 2011);
- Developing a range of updated and new guidances to clarify CDRH requirements for predictable, timely, and consistent product review, including device-specific guidance in several areas such as mobile applications (draft guidance released July 19, 2011) and artificial pancreas systems (draft guidance released December 1, 2011);

- Revamping the guidance development process through a new tracking system, streamlined processes, and, to the greatest extent possible within available resources, core staff to oversee the timely drafting and clearance of documents (December 2011);
- Improving communications between FDA and industry through enhancements to interactive review (some enhancements are already in place);
- Streamlining the clinical trial (IDE) processes by providing industry with guidance to clarify the criteria for approving clinical trials, and the criteria for when a first-in-human study can be conducted earlier during device development. These actions aim to create incentives to bring new technologies to the United States first (guidances issued November 10, 2011) (IDEs are required before device testing in humans that involves significant risks may begin, and they ensure that the rights of human subjects are protected while gathering data on the safety and efficacy of medical products);
- Implementing internal business process improvements to ensure that decisions are made by the appropriate level of management, that decisions are made consistently and efficiently, and that we appropriately apply the least-burdensome principle. For example, CDRH created the internal Center Science Council to actively monitor the quality and performance of the Center's scientific programs and ensure consistency and predictability in CDRH scientific decision-making (Center Science Council established March 31, 2011);
- Creating a network of experts to help the Center resolve complex scientific issues, which will ultimately result in more timely reviews. This network will be especially helpful as FDA confronts new technologies (Standard Operating Procedures issued September 30, 2011);

- Instituting a mandatory Reviewer Certification Program for new reviewers (program launched September 2011);
- Beginning a pilot Experiential Learning Program to provide review staff with real-world training experiences as they participate in visits to manufacturers, research and health care facilities, and academia (to begin in May 2012);
- Providing industry with specific guidance on how to ensure the quality and performance of clinical trials while applying the least-burdensome principle, so that industry conducts studies that are more likely to support the approval of their products (guidance released August 15, 2011); and
- Streamlining the *de novo* review process, the pathway by which novel, lower-risk devices without a predicate can come to market (draft guidance released October 3, 2011).

Our efforts to improve the premarket review programs at CDRH are ongoing. We recently released our Strategic Priorities for 2012,¹⁰ in which we commit to completing or continuing the work we already started in four priority areas: (1) Fully Implement a Total Product Life Cycle Approach,¹¹ (2) Enhance Communication and Transparency, (3) Strengthen Our Workforce and Workplace, and (4) Proactively Facilitate Innovation to Address Unmet Public Health Needs. Our plan for 2012 includes time frames associated with each strategy and

¹⁰ CDRH, “2012 Strategic Priorities,” available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/ucm288735.htm>.

¹¹ A Total Product Life Cycle (TPLC) approach involves making well-supported regulatory decisions that take into consideration all of the relevant information available to CDRH at any stage of a product’s life cycle to assure the safety, effectiveness, and quality of medical devices and the safety of non-device radiation-emitting products. The Center’s TPLC database integrates premarket and post-market data about medical devices. For more information, see CDRH’s website at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm199906.htm>.

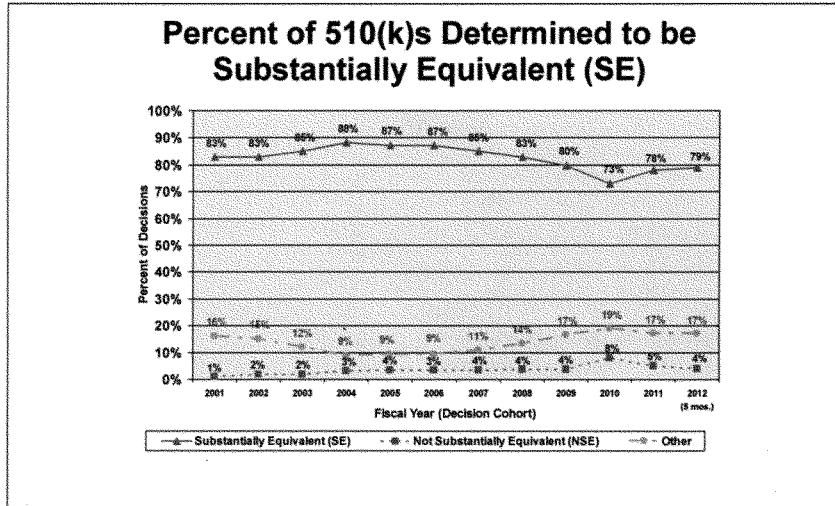
specific actions we will take to meet those goals or make significant progress toward achieving those goals, including, for example:

- By April 30, 2012, begin the Triage of Premarket Submissions Pilot to increase submission review efficiency and better manage the premarket review workload;
- By September 30, 2012, make recommendations on how to adequately recognize good employee performance and address poor performance;
- By September 30, 2012, create processes and tools that will improve the pipeline for innovative medical devices and transform the way CDRH works with medical device innovators, such as the new Entrepreneurs-in-Residence program;
- By September 30, 2012, develop methods and procedures for the systematic analysis and use of medical device recall information;
- By October 31, 2012, develop a comprehensive strategy to assess real-world device performance;
- By December 31, 2012, conduct an evaluation of CDRH staffing, infrastructure, policies, and practices pertaining to medical device software;
- By December 31, 2012, review remaining Class III pre-amendment medical devices;
- By December 31, 2012, fully implement the Experiential Learning Program to enhance premarket reviewer knowledge of how medical devices are designed, manufactured, and utilized by providing real-world learning opportunities; and
- By December 31, 2012, launch the CDRH Leadership Enhancement and Development (LEAD) program to provide CDRH managers and supervisors information and tools to ensure effective leadership.

We believe the actions that we've taken and plan to take in the future will have a positive impact on the device review process by providing greater predictability of data requirements through guidance, reducing unnecessary data requests through training and policy and process changes, implementing policies to appropriately balance benefit-risk determinations, using external experts more extensively (consistent with conflict-of-interest guidelines), creating incentives to conduct clinical studies first in the United States, speeding up IDE approval decisions, and instituting efficiencies in the premarket review process.

For example, I'm pleased to report that, consistent with our many improvements to the 510(k) program, the recent increase in the "not substantially equivalent" (NSE) rate¹² appears to be turning around. For manufacturers and FDA, NSE determinations often represent an inefficient use of time and resources. NSE determinations require significant Agency resources and time, yet fail to result in the marketing of a new product. As shown in the chart below, from a peak of 8 percent in FY 2010, the NSE rate has decreased to 4 percent by the end of the first five months of FY 2012. Just as important, we also may be seeing a reversal in the trend of declining rate in Substantially Equivalent (SE) decisions that clear a 510(k) submission for marketing. After several years of declining percentages, reaching a low of 73 percent in 2010, SE rates increased by 6 percentage points by the end of the first five months of FY 2012, as shown in the chart below.

¹² Among the reasons that 510(k) submissions result in NSE determinations are: lack of a suitable predicate device; intended use of the new device is not the same as the intended use of the predicate; technological characteristics are different from those of the predicate and raise new questions of safety and effectiveness; and/or performance data failed to demonstrate that the device is as safe and effective as the predicate. The vast majority of NSE decisions are due to the absence of adequate performance data, sometimes despite repeated FDA requests.



To best serve patients, both the medical device industry and FDA must have the flexibility to be innovative and entrepreneurial. CDRH must continue making critical improvements to our device program. At the same time, the medical device industry and CDRH must continue to work together to ensure that the Center receives high-quality submissions that contain the information we need to make well-informed and timely decisions. Finally, CDRH must have adequate and stable resources to get the job done right and quickly. Timely reauthorization of MDUFA, as well as the Congressional appropriations process, is critical to achieving these goals.

Moving Forward: Reauthorization of MDUFA

When MDUFA was reauthorized in 2007, Congress directed FDA to take additional steps to ensure that public stakeholders would have adequate opportunity to provide input to any

program enhancements. In addition to FDA receiving input from stakeholders during an initial public meeting¹³ in September 2010, as directed by Congress, we met with stakeholders, including representatives of patient and consumer groups, between January 2011 and February 2012, and made the minutes of those meetings available to the public.¹⁴

During that 13-month period, we also held discussions with representatives of the medical device industry, as required under the MDUFA II statute, in an effort to develop a package of proposed recommendations for MDUFA reauthorization. Minutes of those consultation meetings were also made available to the public.¹⁵

We were pleased to announce that on February 1, FDA and representatives from the medical device industry reached an agreement on the proposed recommendations for MDUFA III. That agreement, which would authorize FDA to collect \$595 million in user fees over five years (plus increases based on inflation), strikes a careful balance between what industry agreed to pay and what FDA can accomplish with the amount of funding proposed. We believe that it will result in greater predictability, consistency, and transparency through a number of improvements to the review process. On March 15, 2012, FDA made public the package of proposed recommendations,¹⁶ requested written public comment on those proposed recommendations, and announced that we would be holding a public meeting at which interested stakeholders could present their views. That public meeting took place on March 28, 2012.

¹³ A transcript of the September 2010 public meeting, and related meeting materials, are available on FDA's website at <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm218250.htm>.

¹⁴ The minutes of the stakeholder discussions on MDUFA III reauthorization are available on FDA's website at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm236902.htm>.

¹⁵ The minutes of the industry discussions on MDUFA III reauthorization are available on FDA's website at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm236902.htm>.

¹⁶ The proposed package of recommendations for MDUFA III is available on FDA's website at <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm292860.htm>.

The proposed recommendations for MDUFA III address many of the priorities and concerns identified by public stakeholders and the device industry and many of the important challenges identified by FDA. Some of the notable improvements to the MDUFA program in the MDUFA III proposed recommendations include:

- **Review Process, Infrastructure, and Capacity Enhancements:**
 - Facilitating earlier and more transparent and predictable interactions between FDA and the applicant, both during the early product development or “pre-submission” stage as well as during the review process, by implementing a structured process for managing pre-submissions and continuing to incorporate an interactive review process;
 - Providing more detailed and objective “submission acceptance criteria” for determining when a premarket submission is complete and when a premarket submission is incomplete and should not be accepted for review;
 - Improving the process of developing, reviewing, tracking, issuing, and updating guidance documents;
 - Recommending reauthorization of the third-party review program and working with interested parties to strengthen and improve the current program as resources permit;
 - Fully implementing guidance on factors to consider when making benefit-risk determinations, meeting with patient groups to better understand the patient perspective on disease severity and unmet medical need, and increasing FDA’s utilization of Patient Representatives to provide patients’ views early in the medical product development process;

- Identifying additional low-risk medical devices to exempt from premarket notification requirements;
- Working with industry to develop a transitional In Vitro Diagnostics (IVD) approach for the regulation of emerging diagnostics;
- Enhancing scientific and regulatory review capacity by hiring additional staff and reducing the ratio of review staff to front line supervisors—FDA is seeking to obtain streamlined hiring authority in order to accomplish this;
- **More Rigorous Review Performance Goals and Shared Outcome Goals:**
 - Adopting streamlined FDA review goals to provide better overall performance and greater predictability, including a commitment to meet with an applicant if FDA’s review of their submission extends beyond the goal date;
 - Eliminating the “two-tier” goal structure of MDUFA II and adopting a more simplified structure, incorporating a single, high-percentage goal for each performance metric;
 - Instituting more rigorous performance review goals:
 - increasing the percentage of 510(k) reviews that are completed in 90 review days from the current 90 percent to 95 percent by FY 2015;
 - increasing the percentage of PMA reviews that are completed within 180 review days, from the current 60 percent to 90 percent by FY 2016, for PMAs not requiring external advisory panel review—for PMAs that do undergo panel review, FDA will complete 90 percent of the reviews within 320 review days by FY 2017;

- Instituting a Substantive Interaction goal for several submission types to track the Agency's communication with applicants at specified points during the review process;
- A joint commitment between FDA and industry to accomplish shared outcome goals to reduce the total average calendar time to a decision for PMAs and 510(k)s so that safe and effective devices reach patients and health care professionals more quickly;
- **Enhanced Metrics for Improvements to the Premarket Review Process:**
 - Conducting a comprehensive independent assessment of the premarket review process to identify potential enhancements to efficiency and effectiveness, and incorporating those findings and recommendations into management of the review program;
 - More detailed quarterly and annual reporting of MDUFA III review program performance.

Additional details regarding the proposed recommendations for reauthorization of MDUFA, including the draft MDUFA III Commitment Letter and Legislative Language, are available on FDA's website at

<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm292860.htm>.

The public comment period for review of the proposed recommendations for MDUFA III began on March 15, 2012, and closed on April 16, 2012. FDA is in the process of considering the public's views and comments, and will revise the proposed recommendations as necessary and transmit a final package of recommendations to Congress, along with a summary of the views and comments that were received and any changes that were made to the proposed

recommendations in response to the public's views and comments. As we continue to work with all interested stakeholders and Congress toward reauthorization of MDUFA in order to provide adequate and stable funding for the program, we will also be moving forward with our ongoing CDRH program improvements, focusing on smart regulation that will facilitate device innovation. As these new policies and processes continue to be implemented, we expect to see notable improvements in the consistency, transparency, and predictability of our premarket review programs.

Smart Regulation's Role in Assuring Patient Safety

As we continue to look for ways to improve our ability to facilitate innovation and to speed safe and effective products to patients, we must not lose sight of the benefits of smart regulation to the medical device industry, to patients, and to society. Smart regulation of medical devices results in better, safer, more effective treatments as well as worldwide confidence in, and adoption of, the devices that industry produces.

We at FDA see daily the kinds of problems that occur with medical devices that are poorly designed or manufactured, difficult to use, and/or insufficiently tested. We appreciate the concern that some devices come on the market in the European Union (EU) before they do in the United States. While we want devices to be available to American patients as soon as possible, consistent with U.S. law, they need to be both safe and effective. The U.S. system has served patients well by preventing devices from entering the U.S. market that were later shown to be unsafe or ineffective.¹⁷

¹⁷ See, e.g., D. Cohen and M. Billingsley, "Europeans Are Left to Their Own Devices," *British Medical Journal*, 342:d2748 (2011), available at <http://www.bmj.com/content/342/bmj.d2748>.

There are significant differences between the EU and the U.S. medical device review systems. In the EU, manufacturers must demonstrate safety and performance, while in the United States, the standard for approval is safety and effectiveness.¹⁸ In the EU, more than 70 private, non-governmental entities called “Notified Bodies” review and approve devices by giving them a “CE mark.” These decisions are kept confidential and are not released to the public or to EU regulatory bodies. In fact, the EU does not have one centralized regulatory body. Instead, each country can designate an entity as a Notified Body, yet the decision of one Notified Body applies to all EU countries.

Because of these factors, it is impossible to track medical device approvals, adverse events, or recalls in the EU, since there are few to no publicly accessible, centralized systems for collecting and monitoring information about medical device approvals or safety problems. The use of Notified Bodies has been criticized as encouraging “forum shopping” by sponsors to identify those Notified Bodies with the most lax operating standards, and the varying levels of expertise among Notified Bodies has been critiqued.

Some have suggested that the United States adopt the medical device regulatory system of the EU. Yet, outside the United States, pressure is growing toward *greater* premarket scrutiny of medical devices. A June 2011 report from the Belgian Health Care Knowledge Centre (a governmental agency that produces studies to advise policymakers when deciding on health care and health insurance)¹⁹ concluded that “[f]or innovative high-risk devices the future EU Device Directive should move away from requiring clinical safety and ‘performance’ data only to also

¹⁸ See “Recast of the Medical Devices Directives: Public Consultation,” available at http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/public_consultation_en.pdf; European Commission, “Guidelines on Medical Devices: Clinical Evaluation: A Guide for Manufacturers and Notified Bodies” (Dec. 2009), at p. 4, available at http://ec.europa.eu/health/medical-devices/files/meddev/2_7_rev_3_en.pdf.

¹⁹ Additional information about the Belgian Health Care Knowledge Centre, and its mission and activities, is available at <https://kce.fgov.be/content/about-the-kce>.

require pre-market data that demonstrate ‘clinical efficacy,’” and “[t]he device industry should be made aware of the growing importance of generating clinical evidence and the specific expertise this requires.”²⁰

In May 2011, the European Society of Cardiology (ESC) issued a “case for reform” of the European medical device regulatory system: that body’s recommendations included creating a unified regulatory system, imposing stronger clinical data requirements, and requiring more accountability for notified bodies.²¹ The ESC cited examples of several different cardiovascular technologies that were implanted in patients in the EU that were later proven to be unsafe and/or ineffective through clinical trials required under the U.S. system and were subsequently removed from the European market.

Also in May 2011, a series of feature articles was published in the *British Medical Journal*, criticizing the opacity of the European medical device regulatory system, and raising concerns about the regulation of high-risk devices and how well they are tested before coming on to the European market.²² Several of the featured articles cited the FDA system’s transparency as helping physicians to make informed decisions about which devices to use and providing patients with access to information about the devices that will be used on them.

²⁰ Belgian Health Care Knowledge Centre, “The Pre-market Clinical Evaluation of Innovative High-risk Medical Devices,” KCE Reports 158 (2011) at p. vii, available at http://www.kce.fgov.be/index_en.aspx?SGREF=202677.

²¹ See “Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform,” Alan G. Fraser, et al., *European Heart Journal*, May 2011.

²² “The Truth About Medical Devices,” *British Medical Journal*, vol. 342, at pp. 1115-1130 (May 21, 2011), available at <http://www.bmj.com/content/342/7807/Feature.full.pdf> (Deborah Cohen, “Out of Joint: The Story of the ASR,” *British Medical Journal* 2011; 342:d2905; Deborah Cohen and Matthew Billingsley, “Medical Devices: European Patients Are Left to Their Own Devices,” *British Medical Journal* 2011; 342:d2748); see also Fiona Godlee, “Editorial: The Trouble With Medical Devices,” *British Medical Journal* 2011; 342:d3123, available at <http://www.bmj.com/content/342/bmj.d3123.full>; Carl Heneghan, et al., “Medical-Device Recalls in the UK and the Device-Regulation Process: Retrospective Review of Safety Notices and Alerts,” *BMJ Open* (May 2011), available at <http://bmjopen.bmj.com/content/early/2011/05/12/bmjopen-2011-000155.full.pdf>.

Most recently, France's Directorate General for Health and its consumer safety body AFSSAPS²³ issued a report²⁴ urging stronger national and European regulation and monitoring of medical devices. In an accompanying statement, France's Minister of Health, Xavier Bertrand, said that EU rules on regulating and monitoring medical devices "must be radically overhauled."²⁵

FDA continues exploring ways to get medical products to patients with serious and life-threatening diseases or conditions faster, but lowering U.S. approval standards isn't in the best interest of American patients, our health care system, or U.S. companies whose success relies on the American public's confidence in their products. We are pleased that a U.S. medical device industry trade association, AdvaMed, has stated that it supports maintaining our current rigorous standards of safety and effectiveness for marketing medical devices: "The medical technology industry has long recognized that a strong and well-functioning FDA is vital to maintaining America's preeminence in medical technology innovation, and we support the current regulatory framework in the U.S."²⁶

Moving Forward

The user fee agreement we have reached with industry strikes a careful balance between what industry agreed to pay and what FDA can accomplish with the amount of funding proposed. The device user fee resource increases contemplated under MDUFA III are designed

²³ Agence française de sécurité sanitaire des produits de santé, France's Agency for the Safety of Health Products.

²⁴ See AFSSAPS, "Poly Implant Prothèse: remise d'un rapport de la DGS et de l'Afssaps aux ministres chargés de la santé – Communiqué," available at <http://www.afssaps.fr/index.php/Infos-de-securite/Communiques-Points-presse/Poly-Implant-Prothese-remise-d-un-rapport-de-la-DGS-et-de-l-Afssaps-aux-ministres-charges-de-la-sante-Communique>.

²⁵ See "France Calls for Europe-wide Control on Prosthetics following PIP Breast Implant Scare," *The Telegraph* (Feb. 1, 2012), available at http://www.telegraph.co.uk/health/women_shealth/9054282/France-calls-for-Europe-wide-control-on-prosthetics-following-PIP-breast-implant-scare.html.

²⁶ Advanced Medical Technology Association (AdvaMed), "AdvaMed Statement on the House Energy and Commerce Subcommittee Hearing on FDA Device Regulation" (July 20, 2011).

to help CDRH meet specific goals. Additional mandates that are beyond the scope of the agreement risk diverting resources from product review, challenging FDA's ability to achieve the new, agreed-upon performance goals.

While we recognize that there are some areas in which legislation may complement the user fee agreement, we note that the success of the user fee agreement rests on enabling CDRH to focus on meeting the ambitious new MDUFA program goals and enhancing timely patient access to safe and effective devices. This is an objective that we share with industry, health care practitioners, patients, and consumers.

CONCLUSION

Over the course of MDUFA II, and especially during the last two years, CDRH has been working, with extensive input from industry and other stakeholders, to take concrete actions toward creating a culture change toward greater transparency, interaction, collaboration, and the appropriate balancing of benefits and risks; ensuring predictable and consistent recommendations, decision-making, and application of the least-burdensome principle; and implementing efficient processes and use of resources. These actions—geared toward a system of smart regulation—have already started to have a measurable, positive impact on our premarket programs, and we fully expect that positive trend to continue as we proceed to implement the improvements we have committed to make.

While we work with industry, other stakeholders, and Congress in the statutory process toward the reauthorization of medical device user fees, in order to ensure adequate and stable funding of the program, we are also continuing to move forward with CDRH program improvements. MDUFA II is scheduled to expire on September 30, 2012, and FDA is ready to

work with you to ensure timely reauthorization of this critical program. If we are to sustain and build on our record of accomplishment, it is critical that the MDUFA reauthorization occurs seamlessly, without any gap between the expiration of current law and the enactment of MDUFA III. At the same time, we must remain mindful that, unlike the PDUFA program in which fees fund more than 60 percent of drug review costs, user fees under MDUFA III (as described in the recently announced agreement) will fund about a third of the total cost of the medical device premarket review process, making it important to keep these resources focused on the performance goals identified in the MDUFA agreement.

Mr. Chairman and Members of the Subcommittee, I share your goal of smart, streamlined regulatory programs. Thank you for your commitment to the mission of FDA, and to the continued success of our medical device program, which helps to ensure that patients and practitioners have access to safe and effective innovative medical technologies on a daily basis. I am happy to answer questions you may have.

Mr. PITTS. The chair thanks the gentleman.

I will begin the question period and recognize myself for 5 minutes for that purpose. Dr. Woodcock, we will begin with you. In your testimony, you say that FDA is expediting manufacturing change submissions to help with drug shortages. In the discussion draft, we include a section on expediting manufacturing changes that will alleviate a drug shortage. In talking with patients and manufacturers and providers, they tell me it is one of the best parts of the discussion draft and it will really help with shortages. Do you agree with those patients, providers and manufacturers that expediting manufacturing changes that will alleviate drug shortages is a good idea? I would like your comments on that section.

Dr. WOODCOCK. We are currently able to expedite manufacturing changes and we do to alleviate shortages or to prevent them if we hear about them in advance. So we do not need authority authorities to expedite a review of manufacturing changes or implementation by manufacturers.

Mr. PITTS. All right. What is the latest on medical gases? We had a hearing on this issue. Will you have a proposal to share with the committee by the end of the week on this?

Dr. WOODCOCK. Well, both parties will have to. We are in active discussions with the association. I have had personal meeting with the association and my staff and there have been multiple additional discussions. I think we are in substantial agreement but we are continuing to go back and forth and make sure we have all the details nailed down, so I can't guarantee, because it is only my side of it, that it will done by the end of the week but we certainly are working very hard on bringing this to a conclusion.

Mr. PITTS. The user fee discussion draft includes language to enhance FDA performance reporting in the drug space by including division-level data. I believe there is great value in regularly gathering and analyzing the best possible data in order to understand where there are working and where they need improving. Collecting more granular information at the review division level will allow FDA management, patients, industry and Congress to better identify where things are working and where improvements are needed. As an example, in November of 2011, the agency issued a report citing the approval of 35 innovative drugs that represented advances in treatment for many serious disorders. If we had division-level data, we could better understand what practices led to such an accomplishment and how we could apply those lessons in other areas. Do you agree that collecting, reporting this information is a good idea given that it will help us understand how we can apply these best practices in other parts of the drug center and agency? Would you comment on that, please?

Dr. WOODCOCK. Certainly. We have calculated the requirements for personnel and investment in generating additional formal reports. We really do believe in transparency of all our processes, and I believe I as a manager am accountable to you and to the public to make sure that we review particularly lifesaving or life-altering drugs as rapidly as possible. It is one of my highest priorities. However, setting up additional reporting systems, we calculate would cost us \$4.7 million based on what is laid out in the draft and

would require 15 FTEs, or full-time equivalents, of people to work on that. Those people would be diverted from working on reviewing the applications.

Now, the division-by-division variability in how many applications come out and how many of those are approved and so forth is primarily a function of the input. So right now, if you looked at it sort of naively, you would say our cancer group is like the most productive group and they do the best job. But they get—right now there is a renaissance of cancer therapies based on the molecular knowledge of cancer that has been generated and so they are able to approve—we are seeing a lot of very good applications and we are able to approve those rapidly.

So I don't think you can make a cause-and-effect link between what comes out in a given disease area and their particular productivity. For example, I think our neurology division is wonderful and does a fantastic job but we haven't been able to approve a lot of new drugs for Alzheimer's because those drugs have failed in development.

Mr. PITTS. The chair thanks the gentlelady. My time is expired.

I yield to the ranking member, Mr. Pallone, for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I am going to start with Dr. Woodcock and may be able to get to Dr. Shuren if there is time. Well, first, welcome back, and I appreciate your being with us again today. I wanted to focus on review times for Abbreviated New Drug Applications, or ANDAs. Under current law, what is the length of time in which the FDA is required to review generic drug applications?

Dr. WOODCOCK. This is like a quiz. I think it might be—

Mr. PALLONE. At least it is not yes or no.

Dr. WOODCOCK. I think it is 180 days.

Mr. PALLONE. OK. And what is the median review time for ANDAs today?

Dr. WOODCOCK. Currently, the average or median or approximately average review time is 30 months.

Mr. PALLONE. And how long do you think it will take to significantly reduce the review times for generic drug applications?

Dr. WOODCOCK. I believe if the proposed user fee program that is put within the discussion draft is enacted, within several years we will be seeing a greatly improved performance.

Mr. PALLONE. And then can we expect to see any meaningful reduction in review times in year one or year two of the generic user fee program?

Dr. WOODCOCK. We will certainly try. However, we have a backlog that comprises almost—there are 2,600 applications in the queue that we have to clear out, and that would be our first priority.

Mr. PALLONE. Chairman Pitts just asked and referred to the discussion draft on PDUFA, and I guess on pages 18 and 19 there is some bracketed language that will require FDA to report to Congress on various statistics about the agency's drug reviews, and I wanted to ask you about this language. Was this part of the negotiated user fee agreement?

Dr. WOODCOCK. Could you repeat the question?

Mr. PALLONE. Sure. I'm talking about PDUFA, and the chairman asked and referred to the discussion draft. On pages 18 and 19, there is some bracketed language that would require the FDA to report to Congress on various statistics about the agency's drug reviews. I don't think that was part of the negotiated user fee agreement, correct?

Dr. WOODCOCK. Yes, that was not part of what we negotiated with the public and with industry, and it was not accounted for in the resource calculations for the user fee.

Mr. PALLONE. So that was my question. I am concerned about putting a burden on the agency that is not funded by user fees and could result in an unwarranted reshuffling of resources that Congress intended to be dedicated to other activities, and I think we need to be careful when we start opening up the PDUFA agreement. I don't know if you wanted to comment on that a little more.

Dr. WOODCOCK. Yes. I believe, as I said, very highly believe in transparency and accountability of the new drug review program to the public, to Congress and to any of our stakeholders. However, we feel these additional tracking requirements when unfunded will divert us from actually accomplishing the objectives that are laid out by Congress in the user fee agreement.

Mr. PALLONE. Now, let me go to Dr. Shuren for a question. I have a couple minutes or less. I wanted to ask you about one of the provisions in the discussion draft related to devices, specifically Section 706 would change the standard for when device manufacturers are required to submit a new 510(k) application for changes to their already cleared devices. It might seem like an arcane issue, but I know it is an extremely important one. Permitting companies to make changes to their devices without first obtaining FDA clearance could result in devices on the market over which the FDA had had very little oversight and knows very little about. Industry of course would say that if they are just making small changes to the device, there is no need to go through the 510(k) process again. But I wanted to get a better sense from you about what is going on here. Is there a need for any change here? Can you speculate on why the language of 706 is being included in the draft, and basically does the FDA have concerns about the language in Section 706?

Dr. SHUREN. We believe the existing standard that we have for modifications is a good one. Most modifications made to a device do not come to the FDA for review. The only ones that come are those that could significantly affect safety or effectiveness. The issue right now is about a guidance we put out on modifications that we did not put out with the intention of increasing in any significant way the number of 510(k)s coming in but provide greater clarity in places that have been gray zones and emerging technologies. We recognize there are many concerns with the guidance. That is why we have had lots of meetings with industry. We have even had two all-day meetings with a group of companies, trade associations coming in the door and raising their issues and working it through. Our intent is to get that guidance right, and we know because of the concerns, our plan is, we would actually put out a new draft guidance and make sure we work it out.

Our concern with what has been proposed in the legislation is it would change the existing approach that we had that had been working for many years, and instead changes it to only submit if it does significantly affect safety and effectiveness. If it does affect safety and effectiveness, you don't submit a 510(k). The product wouldn't come on the market. So essentially companies will be making changes to their devices and none of those changes will be coming to the FDA for review. That causes significant concern. You have devices like linear accelerators that blast radiation at patients to treat cancers. You can now make modifications that can impact that technology, and we won't see it, and we have plenty of cases where companies made changes, they did some testing, and there were big problems that but for the FDA review, those unsafe technologies would have gotten to patients, and that is what we worry would happen with this change in the law.

Mr. PALLONE. All right. Thank you, Doctor.

Mr. PITTS. The chair thanks the gentleman and now yields to the vice chairman of the committee, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. Thank you, Mr. Chairman.

Dr. Shuren, we might come back to the issue of modifications if I have time, but let us talk for a minute about the 510(k) process. It is my understanding that when the Food and Drug Administration clears a device through the 510(k) process, it tells the company that they have received a substantial-equivalence determination and then the FDA sends a letter to the company that expressly states, please be advised that the FDA's issuance of a substantial-equivalence determination does not mean that the FDA has made a determination that your device complies with other requirements of the act, that being the Food, Drug and Cosmetic Act. Is that a correct statement?

Dr. SHUREN. As a paraphrase, and then the company is responsible for assuring they have met what we have called general controls, things that pertain to reporting requirements or labeling or meeting our quality systems or Good Manufacturing Practices.

Mr. BURGESS. If there is a device that is found to be defective that has been approved under a 510(k) authority and another device is found to be substantially equivalent, because of the defect that you discovered in the predicate device, you would do something to prevent that follow-on device from going to the market. Is that not correct?

Dr. SHUREN. What we do in those cases, and there are limited cases, we try to—within our authority we might put explanations in the labeling, try to address it as best we can. The challenge is that those may be ineffective. Right now, there is not a responsibility on the part of the manufacturer to show that if they replicate a design flaw, for example, that they have put in appropriate mitigations to make sure that does not affect patient safety or effectiveness. It has been proposed by some in industry what we would do is, well, you would clear it. They could go to market and then you would build a legal case to say it is misbranded and then take an enforcement action against the company, which kind of puts the cart before the horse. In reality, what we do is clear a device, then maybe take an enforcement action, and what they would have to

do is actually come back in the door with another 510(k). So we do what we can with the authorities that we have but it is not a perfect solution. There is a way of solving it that focuses very narrowly—

Mr. BURGESS. Please let me ask a question so I am sure that I understand it. Right now you are compelled to approve an unsafe device under the 510(k) program?

Dr. SHUREN. Well, compelled to determine that there is substantial equivalence between the predicate and the new product.

Mr. BURGESS. Right. So substantial equivalence, but then that does not necessarily infer that there is approval to market the device under the Food, Drug and Cosmetic Act. Is that correct?

Dr. SHUREN. The terminology, just so we have it right, is clearance. The manufacturer is then responsible for meeting the other requirements of the law to then put it on the market but they do not wait for any other affirmative determination by the agency to go to market.

Mr. BURGESS. This is important, and I am not trying to be argumentative, but has the FDA allowed products that they know to be harmful to reach the market?

Dr. SHUREN. We believe that we have tried to take the best actions we can to assure that the devices that come to market are safe.

Mr. BURGESS. Well, why didn't you just immediately say these are misbranded and must not be marketed?

Dr. SHUREN. So in the few cases where this has happened, we have tried to either address it with labeling and it is our hope that that will be an adequate mitigation. What we don't have in a normal case in premarket review is the data to support that it would be an adequate mitigation.

Mr. BURGESS. Can you provide this committee—you keep saying there are a limited number of examples. We actually need to see those cases. I have to tell you, that concerns me greatly that the Food and Drug Administration for all of the heft that you have has allowed devices to come to the market that may be inherently unsafe that you knew were unsafe before they were marketed. So can you please—how many cases do we have like that? You say there are a few but is it like three or five or nine?

Dr. SHUREN. There are a handful. We will get you some of them. We would be happy to do so.

Mr. BURGESS. All of them, Dr. Shuren. We need all of them because we have to make a determination about where the process is not working because clearly this is—I don't believe you want it and I certainly don't want it where the FDA is approving, because of a finding of substantial equivalence, allows a device to come to market that is inherently unsafe. I don't understand, why would you not issue a mandatory recall immediately?

Dr. SHUREN. Well, first of all, a mandatory recall, if there is a problem, first of all, that we find the problem thereafter. We tend to work with the company for a voluntary recall. A mandatory recall winds up taking—can actually take several years because it involves a formal hearing, and oftentimes we work with the company—

Mr. BURGESS. All I know is, in a medical staff situation, if you know you have a provider, a doctor, who presents a clear danger to patients, I mean, there is an immediate revocation of that person's privileges. I don't see why the same should not apply within your agency in the device world.

Dr. SHUREN. No, I appreciate that, and if folks think that we actually have the authority to do that right now and immediately stop it from going to market, it would be helpful to us then to provide that clarity in legislation.

Mr. BURGESS. Well, and part of the clarity is providing us the cases because that is—Mr. Chairman, I think we may need to involve the Subcommittee on Oversight and Investigations to look into this because this is a fundamental issue of patient safety, and if the primary federal agency charged with providing that drugs and devices are safe and effective is not meeting that first goal, that is a serious, serious problem, and I will yield back my time.

Mr. PITTS. The chair thanks the gentleman and now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Thank you very much, Mr. Chairman. The point Mr. Burgess raised is an important one, and if you feel you need stronger or clearer legislation in that area, let us know because we are concerned about whatever, even a handful of devices that may be harmful.

Dr. Woodcock, I would like to ask you about two proposals designed to help get new important antibiotics to market. One is GAIN and the other is LPAD. First of all, on GAIN, we know the pipeline for new antibiotics is essentially dry. It is a serious public health threat and it is clear that we need to look at ways to incentivize the development of these lifesaving drugs. One way to do that, of course, is to provide additional exclusivity. I think whenever we talk about adding new exclusivity, we need to ensure that it is truly necessary, and in this case, I think a good case can be made that it is, but then it should be narrowly targeted so that only the drugs we need to have developed are rewarded with this generous prize, and exclusivity is often very generous and you never get it back even when it is no longer valid or useful.

I am concerned that the language in the discussion draft does not adequately target, and I want to get your views on that subject. As I read it, the legislation would provide 5 years additional exclusivity to an antibiotic that received FDA approval based only its ability to treat or prevent essentially any antibiotic-resistant bacterial pathogen. I think this legislation should be narrowly targeted and only apply to antibiotics approved for serious or life-threatening diseases for which there is an unmet medical need. I would like to know whether you agree. If so, how would that work in practice? Is that a standard FDA could easily apply?

Dr. WOODCOCK. We do apply a standard on approval on review called the Priority Review, and we determine whether or not a product would be an advance in its class or is simply yet another option amongst multiple options, so we do have some experience in applying some standard like that. I think of course it is up to Congress how you weigh these different tradeoffs as far as the affordability of drugs versus their availability. You don't want to set up

an incentive program, in my opinion, that drives developers toward the broadest market and thus to neglect potentially those challenging areas of, say, drug-resistant organisms, which is where we have the greatest need for new antibiotics. But because that is a narrow market, if you do an incentive program, often the desire is to apply that to the broadest market possible to gain the most obviously profit from doing that. So I think Congress needs to think about what incentive you are offering and how is that incentive going to operate, and will it operate to solve the problem that has been identified. There are several problems. One problem is, we don't have antibiotics—

Mr. WAXMAN. Let me—it is very helpful but then I think about all the things I still want to ask. So you agree that we ought to be sure to narrowly focus this incentive because otherwise an incentive becomes just very beneficial to those who get it but not really solving the main problem that we have. Is that correct?

Dr. WOODCOCK. I believe that Congress ought to define the problem that you are trying to address and make sure you design an incentive that incentivizes drug development to solve that problem.

Mr. WAXMAN. I want to ask you about the LPAD approach. This has been discussed by the Infectious Disease Society of America, and as I understand it, this approach is intended to establish a more rapid regulatory pathway for new antibiotics targeted at the most serious infections. The risk-benefit ratio for such antibiotics will often support more narrowly tailored clinical trials that are needed for other antibiotics. A fundamental aspect of this proposal is that it would require that any antibiotic approved under this pathway bear a strong label statement describing the limited population of patients with serious or life-threatening infections for which the drug had been approved and noting that its safety and effectiveness had not been established beyond this limited population. Companies would have to provide their promotional materials to FDA before distributing them. It seems this kind of approach could really get help critically important antibiotics on the market more rapidly than otherwise possible. However, for it to work as intended and for it not to lead to lowering of the approval standard, it has to have effective mechanisms for ensuring that antibiotics approved for small populations are indeed used by those small populations. I would like to hear your views on whether you think LPAD maintains that balance. Specifically, do you think that it will facilitate the more rapid approval of important new antibiotics for limited populations, and do you think that there are adequate controls to prevent widespread off-label use in a much broader population than for which it was tested and approved?

Dr. WOODCOCK. Yes, and yes. I believe that probably a narrow development program, and we could offer, we believe, a radically smaller development program than for an antibiotic intended for broad uses is a stronger incentive than financial—than exclusivity, number one. And number two, we believe that particularly if Congress were to make a statement about the antibiotic stewardship of this class of products, good stewardship in the market, that that would have the effect of limiting the use.

Mr. WAXMAN. Thank you.

Thank you, Mr. Chairman.

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

Mr. SHIMKUS. Thank you, Mr. Chairman. Thank you all for coming.

Dr. Woodcock, I agree that Congress needs to define a problem we want to address, and that is part of this process of the hearing and also some of the bills that have been introduced. So I couldn't agree more, and of course, I will focus mine on the IDE and the 510(k) issue.

First of all, Dr. Shuren, you said that the number of applicants is down. Is that what you said in your opening statement?

Dr. SHUREN. No, the backlog, so the number of 510(k)s that are still under review at the end of the year has gone down. It had been going up for 510(k)s since 2005 every single year.

Mr. SHIMKUS. OK. Let me follow up then. According to companies who I have talked to, your draft guidance could increase 510(k) submissions by 300 to 500 percent. Do you agree with that? And do you have the capability to respond to that if that is the case?

Dr. SHUREN. So first of all, we don't know if that number is correct.

Mr. SHIMKUS. Have you heard that number before?

Dr. SHUREN. We have heard that number before. But putting aside whether data support that or not, we agree there are concerns with the policy we put out, which is why we are working with industry to make adjustments and try to get it right. Our intent is not to see—

Mr. SHIMKUS. And that is what we are trying to do legislatively also in response to what Dr. Woodcock said that we should define a problem we want to address and we are trying to legislatively address that problem.

Let me go to the IDE real quick, and you have also—a couple concerns. First of all, one is that we do have an issue that we think disregards the Administrative Procedures Act in that it acts as—the guidance contradicts regulation so concern one on that. It also—we do think it also could be not in compliance with the Federal Food, Drug and Cosmetic Act and a former IDE administrator says, and I quote, “It does not look like the authority is there to disapprove an IDE based upon the fact that FDA doesn't anticipate that it would support a marketing approval or clearance.” So the question is, how have innovators reacted to your policy change?

Dr. SHUREN. There have been concerns raised of what we would not consider truly a policy change. Our IDEs, we will not approve if it doesn't provide sound science or if the investigational plan is inadequate. Now, what we said in the guidance is, if it is a pivotal clinical trial and a pivotal clinical trial is intended to demonstrate safety and effectiveness—

Mr. SHIMKUS. The question is, how have the innovators reacted? What have the innovators told you? I can tell you what they have told me.

Dr. SHUREN. So their concern is whether or not this will actually lead to our not approving more clinical studies than before. We think the language may not have articulated clearly what we are talking about. That is namely that if you submit a study that is

producing sound science for its intended purpose, what it is intended to do. In case of a pivotal trial—

Mr. SHIMKUS. Let me—I only have a minute and 40 left. One innovator told me that in 2012, he will only have been in the United States for 5 weeks prior to the first 5 months of the year because he had to do clinical trials overseas. That is what we are hearing from innovators based upon this policy, and I think if the policy is questionable that it is against the Administrative Procedures Act and legally may be against the Federal Food, Drug and Cosmetic Act, I think that would raise some concerns as to the policy which is new and implemented under the last couple of years.

Let me go to funding. In the last hearing, you did talk about funding and the like. Is it true that even under the agreement which doubles the user fees that FDA gets from industry, you will still get about 70 percent of your CDRH budget from appropriations?

Dr. SHUREN. About 65 to 70 percent of funding will come from—

Mr. SHIMKUS. So you will have other non-user fee funds that are appropriated by Congress?

Dr. SHUREN. That is correct.

Mr. SHIMKUS. Shouldn't Congress be able to give direction on how these funds are spent?

Dr. SHUREN. Congress has broad authority to weigh in on how we should actually use our funds.

Mr. SHIMKUS. Thank you. Isn't it true that the FDA undertook activities during the life of MDUFA II that were significant resource investments and outside the agreement? And you probably know what I am talking about, the Institute of Medicine report that was unfinished and not totally accurate?

Dr. SHUREN. First of all, the IOM report, we didn't pay out of any user fee dollars.

Mr. SHIMKUS. Right, and \$1.3 million of taxpayer funds went to the IOM report.

Dr. SHUREN. Well, there were concerns raised on the 510(k) program, how well it was operating to meet the—

Mr. SHIMKUS. But there was obviously concern about the accuracy of the IOM report also.

Dr. SHUREN. Well, we did disagree with one of their recommendations regarding the 510(k) program. We actually agreed with most of their other recommendations.

Mr. SHIMKUS. Thank you, Dr. Shuren. I appreciate your time.

Dr. SHUREN. But I do want to make the point on clinical trials, because it is an important one, and we don't want innovators going overseas, but quite frankly, if we are approving a clinical trial and we are putting our name on it saying that this study is good enough to show safety and effectiveness but it doesn't and it is not going to then support that product coming to market, then we have put patients at risk because they are—

Mr. SHIMKUS. But they are going overseas.

Dr. SHUREN. And then the companies come in the door, and this is exactly what was happening, with studies that then they weren't getting their products approved, and that is the worst thing for the company and it is the worst thing for patients. So the policies we

have put out have actually tried to address the real problem, which is reviewers who are coming back to ask for a study that quite frankly they believe is the better study but that is not the point. It is the least-burdensome principle. They need to put out the study that is least burdensome and approve it. And the second is that they were holding up approvals trying to address questions that were not relevant at that time for making a decision and so draft policy we put out in the fall was meant to readjust that so that we were freeing up and making decisions and approving products. In fact, we are now seeing that first cycle approvals for clinical trials are going up.

Mr. SHIMKUS. And I would just end by saying what I think we have done is moved our innovators overseas, and I yield back my time.

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

Mr. DINGELL. Mr. Chairman, thank you. I commend you for this meeting of the committee and for your fine cooperation in framing this legislation and working with the minority. I also want to express the same commendations to our distinguished chairman.

These questions go to Dr. Woodcock. Please respond yes or no. The heparin incident made it clear that there needs to be robust communications between drug manufacturers and FDA regarding unsafe or compromised drugs. Currently, does the Food, Drug and Cosmetic Act require manufacturers to notify FDA if they have reason to believe that their products have been adulterated, contaminated or misbranded prior to distribution? Yes or no.

Dr. WOODCOCK. No.

Mr. DINGELL. Are drug manufacturers currently required to notify FDA if their drug has been stolen, counterfeited, lost or there have been repeated manufacturing quality incidents? Yes or no.

Dr. WOODCOCK. My understanding is that they do have to notify us for quality problems under field alert reports. The rest is no.

Mr. DINGELL. OK. Now, would requiring drug manufacturers to report such information to FDA confer benefit on the public health?

Dr. WOODCOCK. Yes.

Mr. DINGELL. As FDA continues to regulate an increasingly globalized market, the ability of FDA to work and share information with trusted foreign regulatory counterparts is critical. Do you believe that, and is that a correct statement?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Doctor, is it true that FDA only shares commercial confidential information with State, local or trusted foreign regulators when FDA has written assurance that the agency will not disclose? Yes or no.

Dr. WOODCOCK. Yes.

Mr. DINGELL. Doctor, can FDA currently share trade secret information with State, local or trusted foreign regulators? Yes or no.

Dr. WOODCOCK. No.

Mr. DINGELL. Now, would authority to share this information with other regulators help monitor FDA's efforts to protect the American public with regard to today's globalized drug supply? Yes or no.

Dr. WOODCOCK. Yes.

Mr. DINGELL. Now, would this authority help FDA to have better information to assess risk and target oversight? Yes or no.

Dr. WOODCOCK. Yes.

Mr. DINGELL. Doctor, if given this authority, FDA would commit to only sharing such information with trusted foreign regulators when they have proper and satisfactory assurances that the foreign agency will not disclose. Is that correct?

Dr. WOODCOCK. Absolutely yes.

Mr. DINGELL. Is that necessary for us to do?

Dr. WOODCOCK. Yes.

Mr. DINGELL. I happen to think so. Now, Doctor, so then the agency would not share proprietary commercial information like the formulation of Coca-Cola with China or any foreign country. Am I correct on that?

Dr. WOODCOCK. Yes.

Mr. DINGELL. And FDA would protect that concern and that policy. Is that right?

Dr. WOODCOCK. That is correct.

Mr. DINGELL. Now, Doctor, I have a concern. We have the ability to regulate to some degree the shipment into this country of food, drug, cosmetics and devices. How about the raw materials or the components of this? What is FDA's ability to regulate? Do you have a statutory ability to regulate or not?

Dr. WOODCOCK. We have very limited ability to regulate the supply chain of components.

Mr. DINGELL. Now, I must assume that being able to regulate that kind of activity and that kind of product would be extremely important to assure the safety of American consumers. Is that right?

Dr. WOODCOCK. Yes.

Mr. DINGELL. We found that out in the heparin case, did we not?

Dr. WOODCOCK. We did.

Mr. DINGELL. Now, this committee looked at this problem over the years of safety and that sort of thing, and one of the things that we found is that nobody seems to be able to keep out the admission of illegal substances, unsafe, counterfeits and things of that kind including some controlled substances, and I sense that a part of that, although not all, is the inability of Food and Drug to have the money, the personnel and the necessary cooperative agreements with other regulatory bodies that deal with entry of commodities and people into this country. Am I correct in that?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Do you need additional authority there?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Mr. Chairman, I notice I have used all my time. I thank you for your courtesy.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Michigan, Mr. Rogers, for 5 minutes for questions.

Mr. ROGERS. Thank you, Mr. Chairman.

Dr. Woodcock, I want to thank you and your staff for working with us on the permanent reauthorization of BPCA and PREA. Thank you very much for doing that. I think it has been produc-

tive. I introduced that legislation with my friend, Ms. Eshoo from California, and Mr. Markey, and I think it is representative of good bipartisan work, which is included in the committee's draft today, so I am hoping that other members will join us in supporting that effort. I think they will, and I am proud to say the bill has support of numerous stakeholders, as you know, including the American Academy of Pediatrics, BIO and PhRMA. So I think we are in a good place. We will do good things. And again, I want to thank you and your staff for that. While making these laws permanent, the bill also includes important reforms to encourage earlier submission of pediatric plans, give the FDA new enforcement tools to make sure sponsors meet their PREA commitments and improve FDA's ability to track pediatric studies. I believe our bill strikes that right balance and will improve pediatric drug research, and I hope all members on the committee can support it.

Dr. Woodcock, as you know, there was some language actually authored in 2007 that began the process of developing a standard numerical identifier, or SNI, to help the tracking and tracking of prescription drugs. However, the FDA currently does not have the authority to require the use of SNIs throughout the supply chain. Is that correct?

Dr. WOODCOCK. That is correct.

Mr. ROGERS. So you are familiar with the proposal put forward by a broad group of stakeholders in the drug supply chain on this particular issue?

Dr. WOODCOCK. Yes.

Mr. ROGERS. Great. So if you agree that additional statutory authority is needed to protect the drug supply chain, and I assume you aren't comfortable waiting another 5 years, at least I hope you are not, for the next UFA reauthorization, to create a system that protects patient safety, I would encourage you to roll up your sleeves and sit down with this coalition, and I hope you can do that soon. I think it would be highly productive, and I believe there is a solution here that provides FDA with more authority than it has today but does so in a reasonable, thoughtful way that balances costs and enhancements to patient safety and the supply chain, so I am hoping that we can get a commitment that you will sit down with that coalition and begin that process.

Dr. WOODCOCK. I would be happy to do so, and we obviously need to make advancements in this area. We are seeing, as we saw recently with the counterfeit Avastin and others, we are seeing more incursions of actual drugs that are totally fake into the U.S. drug supply.

Mr. ROGERS. Which is highly concerning, and concerning for you as well. So I look forward to hearing reports on those coalition meetings. Hopefully they will happen soon.

Dr. Shuren, I have some concerns about that new proposal, and I know Mr. Shimkus talked about it a little bit on the 510(k) submissions. It is my understanding that they would have to submit these submissions under your new rules for small manufacturing issues like changing suppliers. Is that correct?

Dr. SHUREN. In a number of cases, it depends. The supplier change may be something that actually doesn't get reported to us.

Mr. ROGERS. But apparently there has been some confusion, but in some cases it would and in some cases it would not. Is that correct?

Dr. SHUREN. Yes, and we can actually get back to you with more details.

Mr. ROGERS. So there are details, so if I read that in total, as a manufacturer I would understand when exactly I have to report or when I do not have to report. Because my understanding is, there is confusion in the way it is written, and if you are on the manufacturing side of that, you are going to have to err on the side of reporting.

Dr. SHUREN. So there are a number of parts in that guidance where confusion has arisen. We recognize that. Our intent in the guidance was to clarify circumstances for submitting a modification because we had guidance out there beforehand and manufacturers were then running into circumstances where we have never addressed the question. They didn't know what to do. Our intent was to actually clarify those circumstances. We recognize there still is a lot of confusion, which is why we have taken the effort to try to work with industry and we will continue to do so to provide clarity that will be most helpful to them, but our goal is not to suddenly raise up the bar and see many more 510(k)s getting in the door.

Mr. ROGERS. But unfortunately, the reality is, that is what is happening and they are going through these processes now believing that they have to do it, so having future conversations aren't really all that helpful.

Dr. SHUREN. Well, it is a draft guidance, so nothing has changed, and that is the whole point of the guidance process. We go out there, we get public comments and we can work this through. That happens all the time. If you actually look at the guidances we put out last year, it is about 44. We heard concerns about maybe three of them in any big way, and that kind of shows the process ultimately works.

Mr. ROGERS. I hear you, but that is the difference between not having to meet a payroll, meeting a payroll, meeting the guidelines for the government that regulates you. They will start to make adjustments based on those guidelines. It will cost them money. They are doing it today, which is exactly why we are hearing from innovators, this isn't worth it anymore, it is easier for me to head overseas than it is to try to deal with what is an untenable regulatory environment. That is what concerns me, and this notion that it is all just fine and it is only guidance and nobody should worry about it is absolutely incongruent with the real world. That worries me greatly, and I hope you will take a hard look at this and come back, and if that is the case, then start making serious indications to the folks who are actually under the gun for this investment to save kids' lives or devices or fill in the blank that you will make that early. Otherwise they are going to have to make these adjustments, and I think that is what you are missing and that is where the frustration is coming from. And I see my time is done, and I thank you, Mr. Chairman. I look forward to hearing about your progress in the coalition's effort to bring manufacturing and clinical trials back to the United States.

Dr. SHUREN. We would be happy to do it. We would actually be happy to come and talk to you in more detail on what is going on with clinical trials. In fact, some of the policies, if you really want to get technology to this country and keep it here, you focus on the very first clinical studies because the innovators have said loud and clear, if there is a good opportunity to start clinical studies here, we bring the technology here, we keep it here, because we keep going back to the same doctors and we put out policy in November to actually make it easier to start those early studies and start it earlier in device development than ever before. The feedback was very positive. In fact, companies have wanted to act under a draft policy, and we have allowed them if they wanted to because they like that policy so much, and we have heard very good feedback from the innovators on that.

For modifications, it is a draft policy, it is not in effect, and we will work with companies and we are happy to come back and give you updates on it to finally get it right, and as I said, this is one where we anticipate we would go out with another draft before even moving to final.

Mr. ROGERS. Thank you, Doctor.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentlelady from California, Ms. Capps, for 5 minutes for questions.

Mrs. CAPPS. Thank you very much, Mr. Chairman, and to our guests, thank you very much for being here today. I appreciate your testimony, Dr. Shuren.

A couple of months ago at our hearing on medical device user fees, I had asked you about the Sentinel system for postmarket surveillance. The PDUFA V agreement allows for postmarket surveillance of prescription drugs through the Sentinel system. However, the same progress has not been made on the device side and the bill draft before us does not address this issue, and that is why I am working on language that would start the process of adding devices to the Sentinel program. I believe this would be a win-win for patients and the industry because patients would gain the security that potential device issues would be found early and recalls targeted to only those devices at risk. Similarly, industry would have the knowledge that data, not newspaper articles, would drive safety decisions. So I am going to have a question for Dr. Woodcock as well, but I would like you to discuss, please, the opportunities for Sentinel in the device base as you see them.

Dr. SHUREN. We think greater engagement for devices in Sentinel could be of tremendous value for not only patients but also for companies as we can identify if there is a problem more quickly so we don't get those big newspaper articles, and even more robust systems that we might be able to leverage in terms of informing for premarket review and ease some of the burden there. The barriers right now, the biggest one is, we don't have there a unique device identifier as we have on the drug side and therefore it is hard to link an actual device with a patient's experience with the device, and we have developed proposed legislation that—regulation—we can't do legislation yet—a regulation that is currently under review by the Administration that will help, and it was helpful when Congress said that Sentinel should be there, should be for

drugs, because it gave a push for people to engage. We don't have quite the same push on the device side.

Mrs. CAPPS. Well, so if we could get some language in this bill that would give you that push, if you will, would that be a value to you and do you see that it is not a one-to-one corollary, I am sure, but there are ways to make it possible for a direct connection to be made, at least some kind of connection to be made from the device to the patient's experience?

Dr. SHUREN. Yes, we do think that could be helpful.

Mrs. CAPPS. I appreciate that. Thank you very much.

Dr. Woodcock, I appreciate your testimony as well. Back in February at our hearing where you testified on generic drug user fees, you and I had discussed the drug shortage problems this country is facing. It is still facing them. It is a very important issue that affected then and continues to affect a great number of people including many of my constituents, and I had shared one story at that hearing. Given the gravity of this situation, I am pleased to see that current legislation now before us includes measures to try to address this problem, but I am concerned that the way the draft is written, it could preclude some health care providers from being involved. Currently, in three separate sections of the FDA user fee discussion draft, the bill lists stakeholders to be consulted with in regards to drug shortages. However, it doesn't specify what kind of stakeholders and health providers like nurse practitioners and physician assistants are notably absent from these lists, despite the fact that the work they do have been affected by drug shortages, in some ways even more directly because they are so much on the front lines. This is evident, for example, in a nurse anesthetist's difficulty in finding anesthesia drugs or an oncology nurse practitioner who is the actual person who dispenses the medication under the doctor's direction and they see firsthand the cancer drug shortages, so would you share with us your thoughts on the kinds of stakeholder engagement with regard to drug shortages?

Dr. WOODCOCK. Well, we believe that we need to hear from the whole prescribing community, which includes a wide range of individuals. Also, the entire pharmacy community is a very important resource for us. So the stakeholders are almost anyone who uses, dispenses, prescribes or manages drug supply in this country and so it is a very broad group of people.

Mrs. CAPPS. And I thank you for that. I believe there is an easy fix here, which I am sort of saying to our committee members to ensure participation and then just including the phrase "all relevant health professionals" not just doctors and hospitals, and that is something you would then agree with?

Dr. WOODCOCK. Yes.

Mrs. CAPPS. That would be useful language to include?

Dr. WOODCOCK. Yes.

Mrs. CAPPS. I appreciate that. Thank you, and I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the gentlelady from North Carolina, Ms. Myrick, for 5 minutes for questions.

Mrs. MYRICK. Thank you, Mr. Chairman, and I thank both of you for being here.

Dr. Woodcock, as you know, the discussion draft at hand makes an effort to further address the drug shortage issue, and I know the FDA is playing close attention to shortage issues as well as working with DOJ on issues of price gouging and stockpiling, but it recently came to my attention that there appears to be a growing problem with drug shortages for trauma and critical-care patients so I have got two questions for you. Does the FDA have a sense of how widespread the shortage is for drugs often used in trauma and critical-care settings, and how do the FDA and DEA need to work together to prevent further shortages in controlled substances used in the critical-care field? For example, are there changes that need to be made to the DEA number assignment system for controlled substances that are being substituted in the event of a shortage or are there other interagency solutions that could alleviate the shortage problem for DEA-controlled drugs, you know, short of an act of Congress, something that you could do internally or with the other agencies?

Dr. WOODCOCK. Well, on the first question, we are well aware that both critical-care settings and trauma settings are being impacted by drug shortages. The shortages are for sterile injectable products, products that are injected directly into, say, a vein or your IV line primarily, and these actually are used in a wide variety and unfortunately very important medical illnesses, very serious and life-threatening illnesses. They are used in ICUs and emergency rooms as well as in cancer treatment, and we are aware of these shortages. We have heard from the professional societies, I have heard personally, and we are doing everything we can. This year we have averted 22 shortages already because we have heard early notification. However, shortages do remain and they are causing serious consequences for the public.

As far as the DEA, we work closely with the DEA. They have a system of allocating materials to companies based on—we provide information to the DEA on projected use for each year as part of their process, and we work with them on shortages, informing them and so forth, but I believe that further discussion of this might require going into more detail, and we would be happy to work with you on that.

Mrs. MYRICK. I would appreciate it very much if you could get back to us because that is an issue I think that there may be some solutions as other people have said with other things.

I have got a second question too. Your testimony goes into some detail about FDA's calculation of risk and benefit when it comes to approving treatments for fatal diseases, and you list a recently approved metastatic-melanoma drug as an example of this risk-benefit approval calculation. It is stated it poses severe and even fatal autoimmune reactions in 12.9 percent of the patients treated yet the drug was approved. The drug is not a cure but, you know, patients successfully treated live much longer than with others. My question is, was this drug approved in tandem with a screening test to distinguish the patients who might respond well from those who might suffer serious autoimmune responses?

Dr. WOODCOCK. No. I think scientifically we aren't there yet to be able to predict that. I am a rheumatologist, and I can tell you

our understanding of rheumatic diseases and autoimmunity is still not as advanced as it should be.

Mrs. MYRICK. Well, would it not be helpful to do some screening test to try and figure out in addition to what you are doing on this issue?

Dr. WOODCOCK. Absolutely, and we support at FDA the concept of personalized medicine. It is simply that scientifically we don't have the tools to develop such a test, and because the patients can develop a wide range of autoimmune symptoms, and to predict each one of those and whether people would develop autoimmunity against their thyroid or their brain or their vessels, we don't have the technology to do that right now. But in the future, that is the future of medicine.

Mrs. MYRICK. Thank you, Mr. Chairman.

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

Ms. SCHAKOWSKY. Thank you, Mr. Chairman, and I want to thank both of you for your testimony.

Dr. Shuren, I want to revisit a topic we discussed at the February 15th MDUFA reauthorization hearing. There had been suggestions that FDA's mission statement should be changed to include things like job creation and innovation, and in fact, the draft House user fee bill does include those changes to the FDA mission statement. And when you testified in February, you spoke about the "unintended consequences" that could lead to "troublesome changes" at the agency, changes that could actually slow down or complicate the review process, not to mention change the standard of evidence for product approvals. You also said that changing the mission statement could even force the FDA to expose confidential industry information, something industry was telling you please don't do, and could require the FDA to review commercial financial records. So I am asking if you could comment on the implications of revising the FDA mission statement to include things like promoting innovation, economic growth, competitiveness, and I am particularly interested in whether you think these should be a part of the core mission of a public health agency. I would also like to know whether these and other requirements in the mission statement might be the basis for lawsuits or other challenges against the agency.

Dr. SHUREN. Well, we do have concerns about some of the changes that would be made to our mission statement, and the highlighted economic growth or job creation is of concern. If this now becomes a part of what we take into account in making decisions, think about approval decisions. Whose jobs are we talking about, the job of the companies coming in with a product and they may get some more jobs or the competitors who may lose jobs? In fact, when there is disruptive technology, many of the competitors, there are shakeups in the market and some of the companies, their product lines go and people's jobs may go. Are we talking about foreign companies? Are we talking about U.S. companies? Are we now taking into account financial considerations in terms of those companies' anticipated market growth or not? Those are things our scientists shouldn't be dealing with. We should focus on science in as-

sure that the products that come on the market are safe and effective, and that is protecting public health and we are also promoting public health, which is already in our mission statement.

Regarding lawsuits, just within the past few months we have had two lawsuits where the mission was cited as one of the bases for that lawsuit, and we do see that coming. So if there are changes to the mission statement, yes, people will use that as a basis for lawsuits.

Ms. SCHAKOWSKY. Thank you. Those changes concern me very much as taking away from the core mission that you have, and I would also like to ask Dr. Woodcock, because the dramatic changes to the FDA mission statement would apply across all product areas including drugs, I wonder if you could also comment on those proposed changes.

Dr. WOODCOCK. I agree with Dr. Shuren. We neither have the expertise to figure out the economic consequences and parse them finally nor—our primary public is the people who take medicines and the people prescribing give those medicines. To them we owe our central obligation of making sure those drugs are safe and effective and they reach them as rapidly as possible. So I see this could have negative consequences.

Ms. SCHAKOWSKY. And you are suggesting that those negative consequences could be patients, industry, the agency. What are your main concerns? I mean, would you view this as a distraction from what you are currently doing?

Dr. WOODCOCK. Yes, and it would be primarily that we would have challenges of our approval decisions based on factors that most people would consider extraneous to whether the product will really help people. That has to be our main consideration, is it effective in the population, is it safe, and if we are asked—that is what I believe we should be focused on: impact on patients.

Ms. SCHAKOWSKY. Well, I agree. I think this would be a dramatic shift in focus and one that really the agency has no historical expertise nor in my view should it. So I thank you and 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 very much.

Dr. Woodcock, welcome back. I always appreciate your candor and information to us. I also want to thank my colleague, Mr. Dingell, for working with us on some of the issues involving GDUFA. And finally, in your testimony, I want to thank you for working on the accelerated approval of Kalydeco for cystic fibrosis. Many of the patients I know in my area are grateful for that. I know it is a small step but it is a significant step, and I think it is an example of why we need to be moving on some things with accelerated action here.

At a recent Senate hearing, you stated—you were talking about the challenges in international factory inspections. Here is your answer. You said there are two issues here. One is the FDA's ability to inspect to inspect those foreign facilities and the generic drug user fee program squarely addresses that, and I will level the playing field and make sure that the intensity of inspection, domestic, foreign, no matter where, will be the same and will be able to use

a risk-based approach to inspection. Now, under the GDUFA goals letter, the FDA says it wants to achieve biannual inspection of foreign plants within 5 years, so here is my two-part question. First, is your answer from the Senate hearing still true, and two, can the FDA achieve parity between foreign and domestic facility inspections within the 5-year \$1.5 billion time zone outlined in GDUFA?

Dr. WOODCOCK. Yes, we believe that the answer is true. I was at a meeting yesterday where we were discussing this with our field organization and the Center for Drugs how we would implement this inspectional program, and we would really look forward to having that global safety net in place.

Mr. MURPHY. Thank you. Now, I should disclose an important generic drug manufacturer, Mylan, is headquartered in my district, and we want to make sure that any inspections they have to go through are equivalent to what takes place overseas. Now, my understanding is that based on the current statute, the FDA inspects domestic plants more frequently because they are looking for so-called “known risks” even if the plant has no history of problems but inspectors don’t have the same body of knowledge about foreign factories because they haven’t been there, and sometimes not in the last decade. So Dr. Woodcock, will you agree that inspectors have a certain comfort level visiting domestic factories because there is a record of inspection history that helps to identify known risks to these factories?

Dr. WOODCOCK. My understanding is that we have a statutory requirement to inspect domestic facilities every 2 years, and that is partly what drives the frequency of inspection. It is also that there is considerable logistical challenges to covering the globe. But the Center for Drugs has a risk-based approach to inspecting facilities. We try to identify the facilities that pose the most risk including the fact that we don’t very much about them and try to target out inspections based on those risks. In addition, we do preapproval inspections, so that drives quite a few inspections because before a drug is released on the market, we want to know that the facility that is producing it and often it is multiple facilities are in compliance.

Mr. MURPHY. Thank you. I am just concerned here that if you go to a domestic factory, you see a problem, you can follow up or even a suspicion something might have happened but if we have long time delays—and I understand the global problems there but it is a concern that there is not the same follow-up. If Congress directs the FDA away from a statutory requirement to inspect facilities once every 2 years and instead allows the agency to adopt a risk-based approach, what factors might the agency consider using to determine what is a facility in need of inspection versus one that may not be?

Dr. WOODCOCK. Well, we currently have a model. Obviously one of them is how recently have we been to the facility and how much do we know about it, and really, the less we know, the more important it is to know more and to visit the facility but also, for example, parenteral drugs that have to be sterile are a higher bar of manufacturing than tablets or capsules or creams, so that is a factor. The number of products that are produced in a facility ups the ante of risk, so to speak, because it is harder. There are more

changes for mix-ups and so on if you have a lot of products made on the line. We have multiple factors like that that are technical on the challenges of manufacturing that go into the calculation as well as the history of the firm—have they been having problems, has that facility had problems in the past. That should prompt more frequent visits.

Mr. MURPHY. Well, thank you. I know that I am just about out of time but I wanted to also note that I am exploring putting guidance into the FDA for placing higher priority on inspecting foreign plants that have not been visited within the last 4 years. I could see this is beneficial for public safety because I think it would establish something of a psychology for plants that haven't been visited in the past 4 years that the FDA might be visiting soon, and I welcome your thoughts on that too, and also, in the goals letter for GDUFA, the FDA estimates that are 2,000 finished dosage form and active pharmaceutical ingredients manufacturing facilities that are associated with generic drug applications. I hope you can get to me in the future and let us know if this estimated all included the FDF and API facilities and does the FDA believe that there are other registered facilities under its jurisdiction that solely support branded applications. I will get you those questions in writing and I appreciate some feedback. Again, Doctor, thank you for your candor. I really respect your comments. I yield back.

Dr. WOODCOCK. Thank you.

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

Mr. MATHESON. Thank you, Mr. Chairman. And Mr. Chairman, I want to acknowledge how you have been working in a bipartisan manner on the reauthorization of this. I really appreciate that.

Over the past several years, I have worked with drug supply chain stakeholders in crafting legislation to develop a national system to better protect our Nation's drug supply against counterfeiting threats. Last year, I introduced legislation along with my colleague, Mr. Bilbray, to address this issue, and I certainly want to thank him for all the work he has done with me on that bill. Recently, a consortium of stakeholders from all sectors of the supply chain have come together to craft a proposal to address counterfeiting and supply chain safety. I am pleased to see that many of the elements of the legislation that I have worked on were included in this RxTEC proposal. I am supportive of this proposal, and I hope to see its inclusion in this year's user fee reauthorization, and I would like to note that the last time this committee attempted to work on a national track-and-trace system, we failed because there was no consensus among the supply chain stakeholders. The FDA has raised concerns over this proposal because it does not mandate a unit-level system by a date certain.

Dr. Woodcock, in your written testimony, you note that Congress should provide FDA with the authority to require a "cost-effective track-and-trace system in order to improve the security and integrity of the drug supply and show transparency and accountability in product manufacturing and distribution." However, many in the supply chain have raised concerns that a date-certain mandate approach would be cost-prohibitive and create a logistical challenge that could actually endanger the drug supply chain. So the ques-

tion that I have for you, Dr. Woodcock, first, how do we ensure that a date-certain approach is in fact cost-effective and does not have unintended consequences such as job loss or further exacerbating the growing drug shortage problem in this country?

Dr. WOODCOCK. Well, to start with, I would like to say again that we need to look at the problem we are trying to solve and make sure that any interventions we take will solve the problems that we are trying to address. My understanding with track and trace is, we are trying to deal with counterfeits, stolen drugs that are re-introduced, recalls, substandard drugs and so forth and prevent them from actually reaching patients and harming people. Our concern about the current proposal by the coalition, we have talked to them. As I said, I am happy to meet with them but that it will not meet the objectives of preventing those problems. It may help—in my analysis, it may help in reconstructing what went wrong after the fact, but if you want to interdict counterfeits and tampered drugs and so forth from reaching patients, then you have to be able to recognize it at the time it is introduced into the system, and so any system, any new requirements that don't accomplish that may not be worth the cost because they may be additional things that people have to do, but if they don't accomplish the objectives of protecting patients, they may not be worth it.

Mr. MATHESON. I am all for looking for the objective but you just mentioned cost, it may not be worth the cost, so I am suggesting that the concerns raised that if you want a date-certain mandate that that is going to have negative cost consequences, and so my question is, how do we evaluate, how do you intend to look at if there is going to be—the cost effect is not going to be a problem here?

Dr. WOODCOCK. Well, we have been looking at this. We plan to develop and are developing voluntary standards that we would put out that people could use and hoping that the technology which many products in the market are tracked this way already, not pharmaceuticals, so hoping that the technology will reach a state where it will be cost-effective and not excessively burdensome.

Mr. MATHESON. I have to admit, hoping technology gets there and seeing date certain, those things in my mind are in conflict. I don't actually think that matches well.

Noting some of the challenges that the California law is facing, I am trying to understand why this date-certain approach would work at a federal level when it has caused difficulties at the State level in California, and should we not look at the types of systems that are feasible across the supply chain system before we decide what and when to mandate?

Dr. WOODCOCK. Well, I do believe that we should look at feasibility, absolutely. However, many of the stakeholders have told us they are worried about having 50 different systems.

Mr. MATHESON. That is why I introduced my bill. I hear you. We need a national standard. I am just trying to figure out how we are going to manage it.

Dr. WOODCOCK. But that means we have to settle on the technology if we do that, and what is going to be tracked and how it is going to be tracked, and that has been difficult because right now the costs have been fairly significant to some of the stake-

holders because they don't do this now. They don't electronically track the products as they move through the supply chain and all the way to the patient. So I agree, there are tradeoffs here, and it will cost money to put such a system into place.

Mr. MATHESON. I will just close by saying I think the RxTEC proposal represents a consensus of a lot of the stakeholders. It does agree on a one-size-fits-all for the country and not 50 different State approaches. And I think we ought to continue this discussion about looking for if there is a way to accommodate this proposal without mandating a date-certain approach.

With that, Mr. Chairman, I will yield back.

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

Mr. LATTA. Thank you, Mr. Chairman, and welcome back to the committee. Great to see you again.

Kind of going in a little bit different direction here. Dr. Woodcock, I know of a number of hospital systems that are coping with the hospital drug shortage by repackaging those drugs into smaller dosages, and these hospitals have also noted that the current law does not allow for the hospital to repackage a drug for use in another hospital within their own system, and we have quite a few systems, of course, not only in Ohio but across the country, and this appears to be an older regulation dating back to when hospitals were typically only in one building before they became the hospital systems. Has the FDA looked at updating this requirement to allow for repackaging within the same hospital system?

Dr. WOODCOCK. I would have to get back to you on that. I do not think that we would object to such practices if they would help alleviate shortages but whether there is a law on the books that is being interpreted as prohibiting that, I am not aware of that.

Mr. LATTA. And again, I am glad to hear that because again, it seems a logical way to help solve it, because again, if one hospital has it, they could get it out to one or others in the same locale. That would be helpful because, again, it would help alleviate those shortages.

Dr. WOODCOCK. If I may interject?

Mr. LATTA. Absolutely.

Dr. WOODCOCK. We allow pharmacy compounding. Usually the hospital pharmacy would be handling these products and they would be the ones to put it into smaller vials or whatever. So that is why I am confused about why they feel that that isn't allowed, and we will get back to you on that.

Mr. LATTA. I appreciate that. And over time, it would help alleviate the problem, because again, we are talking about these shortages, I know you have been here before. We have quite a bit of discussion about that as to how to alleviate it, and when you have the situation that at least in the chain that one of the hospitals has the ability to supply the other ones, it would be very helpful, and so I look forward to your response on that. I would like to get back to these hospitals to be able to say that they can get this done and help alleviate that problem.

And with that, Mr. Chairman, I yield back.

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

Dr. CASSIDY. I always enjoy both your testimonies. Thank you. And as a practicing physician, I respect what you said earlier, Dr. Shuren, that the FDA's obligation is to protect patients' health. I thank you for that too.

I would like to build upon, Dr. Woodcock, our conversation last time which was very good. The last time, I think we agreed that a valid prescription would be important to have, not just for controlled substances as currently but also for non-controlled drugs. So I just wanted to state that for the record.

Dr. WOODCOCK. I agree.

Dr. CASSIDY. Secondly, we also spoke a lot about illegitimate online pharmacies. Now, you had mentioned the VIPPS program, which I had mentioned as a practicing physician married to a physician we did not know about, but since then we have kind of looked at it. I gather that this, although a good effort, only has about 30 pharmacies listed even though it is estimated there are about 1,500 legitimate pharmacies and just an explosion of illegitimate pharmacies. And secondly, that we still have, despite our conversation last time, there continues to be reports of adulterated drugs causing harmful effects to patients here in the United States. So with that said, Representative Ross and I in a companion bill to something that Senators Feinstein and Cornyn and others have introduced on the other side have an online pharmacy bill requesting that FDA compile a registry of legitimate online pharmacies so that I as a doc or I as a patient or I as a dad of a patient could log on and see, is this a legitimate online pharmacy. I gather FDA has some objections to that. Could you kind of go through those objections?

Dr. WOODCOCK. Certainly. Basically there are practical difficulties in us doing that. As you said, there is a huge plethora of pharmacies that are probably not legitimate that consumers do order their drugs from and often they have no assurance that those are actual drugs.

Dr. CASSIDY. That is why we have the bill.

Dr. WOODCOCK. Yes, so we are in agreement on the problem. We have trouble certifying Internet sites that would be legitimate. We have difficulties—

Dr. CASSIDY. But see, the National Association of Boards of Pharmacy, the NABP, currently does that.

Dr. WOODCOCK. Yes.

Dr. CASSIDY. So why can they do it and the government cannot, or why could you just not contract with them to ask them to do it?

Dr. WOODCOCK. I think it is worth discussion on how to establish a broader list of legitimate pharmacies. It is another work stream that we don't actually understand how we could accomplish very well.

Dr. CASSIDY. Now, in our bill, we allow you to contract that. I mean, I can tell you, Google can tell you who is legitimate and who is illegitimate, you know, Google, the big Internet—

Dr. WOODCOCK. I know Google but we are talking about a pharmacy here and so—

Dr. CASSIDY. But they advertise via Google, and so I suspect that—I mean, it is not an impossibility to do it. You may not have expertise nor I but I promise you, NAPB has that expertise, and our bill allows you to contract out to them. Why not?

Dr. WOODCOCK. Well, we are not sure that a certification by the federal government could—it would have to be very frequent inspection of the distribution center because you have a web page but there is not necessarily a brick-and-mortar entity behind that.

Dr. CASSIDY. Now, in there we do require to have some sort of U.S. asset, and we have spoken with NABP. Obviously, we weren't concerned if someone could come in as legitimate and flip to being rogue.

Dr. WOODCOCK. Exactly. That is one of our concerns.

Dr. CASSIDY. NABP says that has never occurred in their experience.

Dr. WOODCOCK. Of course, they only have 15 in there.

Dr. CASSIDY. Thirty. That said, at some point we have to move beyond existential fear, oh, my gosh, we don't know all the unknowns, and say if we are going to protect patient safety and we know this is an incredible problem, let us embrace the fear, if you will. Again, why do we allow existential fear to paralyze our efforts to protect our patients?

Dr. WOODCOCK. I don't think it is existential fear. I believe that we are having difficulty conceiving of how we would add this program to our existing programs. So we would be very happy to work with you on this and talk to you about it.

Dr. CASSIDY. I would love it if you would support the bill because we will contract this out and there is someone out there that can do it, which I think is a logical thing. Someone out there knows how to do it even if the federal government doesn't. When I go through TSA, they know everything about me. To think that we can't figure who is legitimate and illegitimate just seems not quite to make sense to me.

I have 2 seconds left but you have been giving everybody slack. Can I quickly ask one more question?

Dr. Shuren, the unique identifier that has been suggested for medical devices, it is my understanding it has been held up at OMB for 5 years. That is what I was told. Maybe it not 5 years, maybe it is a shorter period of time. But even at the glacial pace at which government works, that seems a way to take a proposal and never get it out. Any thoughts about why OMB is holding up a unique ID system which really could help us improve safety of medical devices?

Dr. SHUREN. It is probably a question best put to the Administration. I will say the rule has been under review since July of 2011, so not 5 years.

Dr. CASSIDY. Oh, good. I am comforted by that.

Dr. SHUREN. Well, sometimes when people hear that things take longer, sometimes it is not always correct.

Dr. CASSIDY. OK. So any idea? Is there ongoing discussion or is it just a wall of silence? Do you have any sense of is progress being made on this?

Dr. SHUREN. We continue to engage with OMB. We certainly believe it is important to have a unique device identification system

in place in the United States. It will be critical to have a robust postmarket surveillance system. It will help in terms of recalls and adverse-event reporting but can also allow us to have a system in which we may get sufficiently good data that can be used to support new products coming to market. So it is not just about better understanding of benefit-risk profile once out the gate. It may actually be able to help companies in reducing the new evidence they need to generate to bring a new device to the United States.

Dr. CASSIDY. I yield back. Thank you.

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

Mr. GUTHRIE. Thank you, Mr. Chairman, and first, Dr. Shuren, I just have a comment. I know we have met in my office over medical device approval processes. I thought that was a very good, productive meeting, and you have talked today about the first-time approvals or the innovators and the least burdensome and getting it right, being safe and effective, but also efficient. I think that is important. I appreciate that, because it has been a big concern of mine that we are having people go overseas to get their products approved but not going to the least common denominator, going to the European Union and other areas and trying to get approved. And so we are interested as oversight monitor how that goes forward and appreciate your openness in meeting on that.

Dr. Woodcock, there is a question I have. I talked to anesthesiologists and anesthetists and of course in the childcare cancer drugs of the shortages. When there is a shortage in a drug, I guess you can go to an alternative source if a manufacturer can't produce the drug. How does that process work? How do you actually make that happen?

Dr. WOODCOCK. We hope usually we would get early notification from a manufacturer that they may be having to go out of production or reduce production and not meet the supply. We will then look around to all other manufacturers who have ever made that drug and see if they can ramp up so that we would avert the shortage. If that doesn't happen, then we might look outside the United States to people making a comparable drug elsewhere and we would check with other regulatory authorities to make sure their production was proper and the history of the drug so make sure we are not introducing a substandard drug into the United States, and then we would allow importation of that drug to cover if a shortage actually developed and we would talk to that manufacturer.

Mr. GUTHRIE. Is there a formal process for that?

Dr. WOODCOCK. A formal process?

Mr. GUTHRIE. A formal process. Does somebody have to notify you when they know they are not going to make shipments and things like that or it is something that you have to react to?

Dr. WOODCOCK. Well, there is some requirement to notify us but of course there is interest in more formalizing that notification process, and we think that would be helpful.

Mr. GUTHRIE. And I have had people talking about having to delay surgeries for anesthesia and childhood cancers. Those are the two I mentioned. I know there are others. But since you have a handful that seem to be the bigger issue, do you have like a list

of the people that can come online when you need to get them online?

Dr. WOODCOCK. We have done extraordinary efforts to try and deal with this situation. The problem is that these are sterile injectables. There were only a few facilities in the United States that made these. They made large numbers of products so hundreds of products, and they had problems that they had to take their production offline and it almost sort of happened—it was like a perfect storm of problems. So we are having to look elsewhere and we are working with them as closely as possible to try to bring them back up into production of these medically necessary drugs.

Mr. GUTHRIE. Do you think it would be helpful to have some kind of program that maybe manufacturers could voluntarily participate in? I know there are some areas you are just going to get blindsided because something happened in manufacturing. I know sometimes things happen in a manufacturing facility. But do you think if there would be a more formal program that maybe companies could volunteer to participate in, manufacturers could that could react quicker or do you think—

Dr. WOODCOCK. We have heard from the private sector, and they are putting together some efforts on exchanging information and providing better information to us, and we think that things like that would help also. I would stress that we already have the flexibility. We will allow the manufacturers to continue in production even if they are having manufacturing problems. Maybe they will release batch by batch. We have even had manufacturers sent a filter with the product that had particulates in it which can't go into your veins, but we let them put a filter in after tests showed that would work and shipped that with the product so that that product so people could have anesthesia or they could have their cancer drugs. So we have a lot of flexibility. We do a lot of things now but it would probably help us to get more information earlier.

Mr. GUTHRIE. OK. Thanks. I appreciate that very much, and I yield back.

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

Mrs. BLACKBURN. Thank you, Mr. Chairman.

Dr. Shuren, I had a couple of questions for you. I really wanted to follow up on a letter that some of my colleagues and I sent to you earlier regarding the wireless medical devices and the mobile medical applications. You have talked a little bit about bringing technology and keeping technology-based jobs here in the country, talking to innovators. So I wish that you would take a couple of minutes and just detail what primary activities related to wireless health services and health devices are underway at the FDA including the independent and jointly with the FCC and the ONC, if you will, if you will just talk about what is underway there. And then I would also like to know who is tasked, if you have got one person that is tasked with overseeing the policy development in this area looking at regulations, guidance, documents, etc.

Dr. SHUREN. Certainly. For wireless technologies specifically, we are working on guidance to provide greater clarity to industry. We know this is a booming market and we want to make sure that

innovators have the information they need to help bring those products to market. We have been working with the FCC. We sort of have split responsibility because they oversee what spectrum may be available and then we assure that when we are dealing with medical devices that they are safe and effective and so we have been getting together periodically to assure this good coordination where there are those areas in which we engage and to also make sure that we stay out of each other's way.

Mrs. BLACKBURN. And do you have one specific point person that is handling that?

Dr. SHUREN. The person on our end who handles that engagement is Bakul Patel, and he is in my office.

Mrs. BLACKBURN. OK. And then is he handling the intra-agency coordination as well as the interagency?

Dr. SHUREN. Yes, that is correct, so one person.

Mrs. BLACKBURN. So he is the guy in charge basically on that?

Dr. SHUREN. So to speak, yes.

Mrs. BLACKBURN. And then could we get a listing or a memo that would give us more or less the primary activities related to these wireless devices that are underway? Could you give us a little bit more information or guidance on that? And you can submit that in writing.

Dr. SHUREN. We would be happy to do so. We can also provide more information regarding medical apps, an area where I think you know we took a position that while many of these apps could be under FDA authority, we actually made the decision that you know what, for the majority of these, they shouldn't come to us even if they should as a matter of law and we are willing now to——

Mrs. BLACKBURN. So are you traveling then with your guidance to which—and this is one of my other questions for you. Realizing that there is a difference between medical devices and medical software, are you moving that direction to being able to provide that guidance?

Dr. SHUREN. So there is also guidance on clinical decision support software. Some software has been regulated as medical devices for years. What we are doing is going back for those kind of software to say some of these things, you know what, we shouldn't even look at even though they might fall under our purview and a lot of things that otherwise we would, we are going to come out with a policy that says we are leaving you alone.

Mrs. BLACKBURN. So you are adjusting what would and would not fall under the Drug and Cosmetics Act of 1970?

Dr. SHUREN. We are going even further to say even if you fall under it, we may go out and say we will exercise enforcement discretion, don't worry about it, you don't have to come to us. We are going to narrow actually our purview even further than what the law may otherwise say. We are trying to adapt to the emerging technologies and adapt our approach to the business models for software, because we realize that even in those cases where it comes to us, you can't apply a traditional approach. There needs to be the ability to make frequent updates and for us not to get in the way of that technology.

Mrs. BLACKBURN. OK. Should we as legislators go in here and update the definitions of devices and software based on those advances in technology that you just touched on?

Dr. SHUREN. We don't think there is a need for it, and, you know, one of the challenges is, when you make the change in statute, it winds up having broad ramifications. It is very hard to put in something that applies the appropriate touch, if you will, and that is why we are able to do through a public process with policy changes where we can—

Mrs. BLACKBURN. OK. Let me ask you this then. You just talked about some of the software updates. I get notices for updates for different software packages all the time. I mean, it seems like almost a daily occurrence. So would each update that goes out, if it is under your jurisdiction, would each update need a separate approval process, or how do you envision that working?

Dr. SHUREN. No, and in fact, we are kind of looking to have an approach where you can make those kind of routine changes in software and not have to bother coming to us. It would only be certain things where you really change the technology itself and what it was about where that is an issue, and even there, the universe where we are going to be focusing is very, very narrow, even though more things might fall under our purview, so we are truly restricting where we would focus, and at the end of the day there is the value added, but you will see that the majority of the stuff out there, our intent is to just leave it alone.

Mrs. BLACKBURN. OK. Thank you. I yield back.

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

Dr. GINGREY. Mr. Chairman, thank you very much.

I will address my first question to Dr. Woodcock. First of all, let me apologize for coming in at the last minute. We had a concurrent hearing that I chaired, so I apologize for that.

In reference to antibiotic shortages in general and specifically the GAIN Act in particular, I know that my colleague on the other side of the aisle, the ranking member, Mr. Waxman, had talked about that a little earlier this morning in regard to this limited population antibiotic drug proposal. Staff at FDA told my staff just this Monday that the FDA has not officially endorsed the LPAD, if you can call it that, that proposal. Has the FDA officially endorsed the Limited Population Antibiotic Drug proposal as part of the GAIN Act or in any way?

Dr. WOODCOCK. Well, the Commissioner, Dr. Hamburg, and I have talked about this, a program like this to many different stakeholders so we certainly feel that is something that should be considered by Congress. But if course, there is nothing specific in the GAIN Act right now that reflects this proposal. So we do feel that it would be beneficial. The GAIN Act provides long-term incentives for companies to move back into the antibiotic space. A shortened development program, a very narrow development program would provide that short-term incentive. In fact, I have already heard from a company that has written me a letter asking if they could be designated as one of these products because they would be interested in entering that space if they had a very clear development path to market.

Dr. GINGREY. Well, I understand, and you said that you and Dr. Hamburg have discussed it and certainly I am not saying that the proposal does not have merit. I am just suggesting that at this late date, industry has some concerns in regard to making this part of the GAIN Act and subsequently of course part of PDUFA. I wanted to very specifically ask, and I will do that one more time. The FDA has not officially endorsed this. Is that correct?

Dr. WOODCOCK. Well, the Administration has not put forth a proposal.

Dr. GINGREY. Thank you very much, Dr. Woodcock.

Dr. Shuren, there is a line in the FDA industry agreement that reads "The FDA proposes to work with industry to develop a transitional IVD, in vitro diagnostics, approach for the regulation of emerging diagnostics." Dr. Shuren, explain to me what this means exactly.

Dr. SHUREN. Well, actually this is something that industry put on the table, and they put it after 13 months of negotiation back and forth. It actually came up in our second to last meeting, so it was at the very end. And even though we have committed in MDUFA III to talk about it, we have actually already been meeting with industry on it. What we have seen is to date a very broad brush proposal that needs a lot of work but we will work with industry and MDUFA III in putting it forward, and the broad brush strokes are for certain IVDs yet to kind of be determined. Would they come on the market under a lower standard than currently is in place for products to get on the market in the United States with the requirement that they provide the additional data to show that they are ultimately safe and effective at a later date in time, and if not, to then come off the market. Those are the broad brush-strokes. One of the issues we will also have to wrestle with are the implications for the FDA because even if we went down that path, it involves two reviews and two decisions on the part of the FDA for every single one of those devices going through as opposed to the one review and the one decision, and those kind of resource applications we didn't address in—

Dr. GINGREY. Let me ask you this, Dr. Shuren. I am about to run out of time. I have one other question I wanted to ask. Does the FDA see the benefit and support transitional pathway approaches? Do you believe that such a pathway can benefit patients and industry?

Dr. SHUREN. Right now we need to work with industry on exactly what this is and what the ramifications would be.

Dr. GINGREY. Will you keep the committee updated on the talks with industry in these coming months?

Dr. SHUREN. Yes.

Dr. GINGREY. I very much appreciate that. And real quickly, Mr. Chairman, get it in under the line, and this is also Dr. Shuren. A review of the Office of Device Evaluation's annual report shows a decline in the percentage of IDEs approved on the first IDE review cycle. They dropped actually from 76 percent approval in fiscal year 2000 down to 56 percent 9 years later, 2009. What is the explanation for the huge drop in IDEs approved on the first review cycle between 2009 and 2010? And real quickly, is it true that with each new review cycle, a company must pay an additional user fee for

one product and these multiple review cycles are a strain on the FDA's valuable time and resources?

Mr. Chairman, thank you for your indulgence, if maybe Dr. Shuren could quickly respond to that.

Dr. SHUREN. Certainly. There are no user fees tied to the review of IDEs, so we don't get any additional funding from industry for that. What has happened over time, and this is what we are addressing, is that we have got cases where we were not consistently applying the least-burdensome principle. So a decision was held up because a reviewer might be coming back to say we think you should be doing a better study when in fact the study was really good enough for its intended purpose moving forward. And the second is where approvals were being held up to get answers to questions that either did not need to be answered at that time, it may be something for later on, or there were questions that it would be nice to know but we don't need to know it, and that is why we put out draft policy in November of 2011 to sort of free that up to lay out very clearly here are all the different circumstances where we should approve that trial and these are other issues that can be put off to later, in fact, allowing for some cases where we never would have let the trial go through even in the past where we might actually do a staged approval, let some patients come in, make sure there is good data for safety and let it move forward. That is the kind of flexibility we are trying to—

Dr. GINGREY. Well, I am real encouraged to hear that response, Dr. Shuren. Thank you.

Mr. Chairman, thank you for your indulgence.

Dr. SHUREN. And if I can just add that the IDE first cycles have dropped. This year in 2012, they have actually been going upwards for the first time.

Mr. PITTS. The chair thanks the gentleman. That concludes the subcommittee questioning. We have a couple of members on the full committee who would like to ask questions. Without objection, we will go to them at this time.

Mr. Markey from Massachusetts, you are recognized for 5 minutes for questions.

Mr. MARKEY. Thank you, Mr. Chairman and Ranking Member Pallone, for allowing me to participate in today's legislative hearing. I also thank you for including the bipartisan Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act that I was proud to work on with Mr. Rogers and Ms. Eshoo, and I look forward to continuing to work on these important bills.

Dr. Shuren, I am concerned that the current discussion draft misses an important opportunity to improve the safety of medical devices. If a car is recalled because it had faulty brakes, no consumer would want to purchase a new car with the same brake problem. Yet when it comes to medical devices that are implanted in patients' bodies, companies can and do base their products on faulty predecessor technologies. The definition of insanity is doing the same thing over and over again and expecting a different result, but when it comes to medical devices, we have an insane policy that makes no sense. Devices have been recalled because they severely injured patients and they are used again and again as

models for new devices with devastating, life-altering consequences for the patients who are injured by them.

In fact, just last month, I issued a report that documented this problem in detail and shared the stories of patients whose lives were destroyed as a result of this federal loophole. Under current law, the vast majority of medical devices are not required to undergo clinical testing in humans before being sold. Instead, companies need only prove that their new device is substantially equivalent in technology in use to a device that FDA has previously cleared, known as the predicate technology. As we heard, Dr. Shuren, from your exchange with Dr. Burgess, if the device proves to be substantially equivalent to a device that is now known to be defective, the FDA has no choice. The FDA is legally obligated to clear that product for market. The law does not clearly provide the FDA the authority it needs to protect patient safety so that new victims are not created from a technology that we already know is defective.

Dr. Shuren, if a new device proves substantial equivalence to a predicate technology that has been voluntarily recalled for a serious design flaw that could seriously injure people who used it, would FDA have the legal authority to reject that application?

Dr. SHUREN. We would have to find that it is substantially equivalent but we will then look for other opportunities to clarify this, use other mitigations to address it and protect the public. The challenge becomes more about having the ability to just get information.

Mr. MARKEY. But if you found that it was substantially equivalent, would you be able to reject it?

Dr. SHUREN. Not for purposes of substantial equivalence determinations.

Mr. MARKEY. You could not reject it even though you knew it was defective. Is that correct?

Dr. SHUREN. That is correct.

Mr. MARKEY. Well, what if the FDA had knowledge that the new device repeated the same flaw as the predicate technology? Would the FDA still be required to find it substantially equivalent?

Dr. SHUREN. We would have to find it substantially equivalent. We oftentimes with the company at least try to look for changes in labeling or other things that—

Mr. MARKEY. But that would be voluntary? You would not have the legal authority to reject it. Is that correct?

Dr. SHUREN. That is correct.

Mr. MARKEY. Now, the device industry argues that FDA has complete authority to assure the safety and effectiveness of a product including demanding clinical trials when they deem it necessary. Is that true in a case where the product has been shown to be substantially equivalent to its defective predicate technology?

Dr. SHUREN. No.

Mr. MARKEY. You do not have that authority?

Dr. SHUREN. We don't.

Mr. MARKEY. Does FDA currently have any authority to invalidate defective predicate technologies?

Dr. SHUREN. So to invalidate a predicate where there is a problem, we would either rescind the 510(k) as a matter of law. We

could do that, a mandatory recall, or of by judicial order the device is found—

Mr. MARKEY. So you can only do something after the fact, labeling, etc. right? That is what you can do? But you can't reject it. Is that correct?

Dr. SHUREN. Yes, and the labeling we will do before the product comes on the market.

Mr. MARKEY. Does FDA—some have argued that to get around the lack of authority, FDA could just issue more mandatory recalls, thereby invalidating the defective device as a predicate. Why is that not a feasible response?

Dr. SHUREN. If there is sufficient justification to do a recall, we would actually work with the company on a voluntary recall, and companies generally comply with it. To run to a mandatory recall is profoundly resource-intensive, and because there is a formal hearing that can actually take years to do.

Mr. MARKEY. You are saying it is a huge resource drain, not often the best use of FDA's limited resources, but a device recall voluntarily is still available to be cited as predicate. Is that not correct?

Dr. SHUREN. No, that is correct, and quite frankly, it is not a case of necessarily that predicate shouldn't be out there to be used as a predicate but rather having the ability to assure that if there was a problem, one, it is either not replicated in the device, or if it is replicated, there is adequate mitigation, and right now while we can try to work with the company—

Mr. MARKEY. Final question. Would you like—

Dr. SHUREN [continuing]. Having the ability to—

Mr. MARKEY [continuing]. The authority to reject certain devices if they repeatedly had the same dangerous design flaws as other previously recalled defective devices? Would you like that authority?

Dr. SHUREN. We would be happy to work with the committee on what may be the best approach on how to deal with those—

Mr. MARKEY. Would you like to have the authority or not have the authority?

Dr. SHUREN. We would like to have appropriately tailored authority.

Mr. MARKEY. OK. Great. I think I would like to work with you to hopefully accomplish that goal so you do have that appropriate authority.

I thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from California, Mr. Bilbray, for 5 minutes for questions.

Mr. BILBRAY. Following up on that line of questioning, Mr. Chairman, if you had an inhaler, let us just say an insulin inhaler, that was a new model that could be produced cheaper and was smaller than the original but gave the same dosage, same reliability, it was a different design but basically the outcome to the patient was the same. Do we have the ability to say yes, that is comparable, and thus you don't have to go through the entire review process over again?

Dr. SHUREN. It depends upon the changes you make. If those changes made would not significantly affect safety and effectiveness, then you don't have to—

Mr. BILBRAY. Basically, my point is, you have two little devices. One is this big and one is this big. Your doses are the same, the same insulin is being used, it is just a different—basically has been upgraded. You get a call from a flip phone or you get a call from an iPhone, same product, same delivery, different ways of doing it but the same deal. Do we have the ability for you to say OK, this is comparable and thus we can allow it to move forward or does the iPhone now have to go through the whole thing, the review process all over again?

Dr. SHUREN. So for some changes, size actually could affect safety and effectiveness. If it does, that modification comes to us. So you have things like certain joint replacements that when you change the size, that can actually affect—

Mr. BILBRAY. That is inside the body, though. I am talking about an external—

Dr. SHUREN. So some of the other things that may change in size—

Mr. BILBRAY. Like bringing an inhaler down from the size of a liter bottle down to the size, you know, smaller than a lighter. Do you have a comment on that?

Dr. WOODCOCK. Yes. We have a lot of experience in inhaled drugs, regulating them, and—

Mr. BILBRAY. Well, I have a lot of family members that have that same problem, but that is a different issue.

Dr. WOODCOCK. So the problem with the inhalation devices is that we do not have a good way to determine bioprevalance, and that has hampered us in fact in improving generics of, say, asthma drugs that are out there because we can't determine whether they deliver the same dose as the innovator, so that is the real question, OK. So if you move from one inhalation device to another, it may be the same plume—we do plume testing which is particle size, distribution, right? However, the user interface is very important in inhaled devices because some people—you know, we had some devices they were using upside down or sucking on the wrong end, and so there are a lot of issues with user interface with inhaled medicines that influence whether or not how equivalent we can determine them to be another version.

Mr. BILBRAY. Dr. Woodcock, the question that us Californians are talking about, and it has been a few years, the State of California is going to start putting mandates on the issue that had been talked about before, and that is the pedigree issue or the tracing. The fact is, they are talking about going to requiring every unit to be tagged and identified, and we are hearing from a lot of manufacturers that there is just no way they can follow that physically or cost-effectively. What is the possibility of us working on a compromise proposal with being able to trace lots and at least start the process down the road sooner rather than waiting for the crisis that is coming down the road in a couple years when you have a State like California that controls over 12 percent of the market, probably almost 20 percent of the market all at once starting to have a standard that the rest of the country doesn't have?

Dr. WOODCOCK. Well, number one, we agree that it is better to have uniform standards than develop 50 different standards, which would be a nightmare. Number two, you have to, I think, determine what problem you are trying to solve and then see if your solution will address the problem that you are trying to prevent or solve, and then think about how much it would cost to implement it and then you decide the tradeoffs between the costs and the investment you have to make and the benefits that it will bring. We are concerned that the coalition's proposal doesn't provide enough benefits to justify doing that, but you need to think about what else could be done, and I think we are willing to work on that.

Mr. BILBRAY. Are you willing to commit to work on that within this year so that we get some definitive approach or at least some unified strategy on this issue within the year?

Dr. WOODCOCK. I am certainly willing to sit down and work with the coalition on this, absolutely.

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

Mr. PITTS. The chair thanks the gentleman. That concludes the questioning. We have one follow-up on each side. We will go to Mr. Pallone for 5 minutes for follow-up.

Mr. PALLONE. So Mr. Chairman, I would like to yield time to Mr. Markey.

Mr. MARKEY. It would be just Dr. Shuren, if you could. I had a woman that I brought to Washington and we had a press conference about 2 weeks ago, and it was a bladder mesh that she had surgically inserted into her body, and she was assured that it was safe and had been FDA approved, and since then, because of that faulty bladder mesh, she has lost her livelihood as a truck driver, had to undergo multiple corrective surgeries, and because of the medical bills is now being foreclosed upon by the bank, and she has a mother who is living with her, an elderly woman, and there are thousands of other people who have had this faulty bladder mesh inserted in them as well and it is all FDA approved because you cannot reject something that is based upon this predicate technology.

So maybe you could explain a little bit about what happens out there in the real world because the FDA does not have this authority to protect women like that and thousands of others like them that have FDA approval on a technology that has a defect in it that you know about but you cannot take off the market.

Dr. SHUREN. First of all, we empathize with that patient and for other people who may have had adverse effects from medical devices. I will say in the case of surgical mesh, generally the issues we are dealing with may be more of, are they in the right regulatory framework, and we just went through in the case of surgical mesh for pelvic organ prolapse where in fact we held an advisory panel meeting to say should these actually be 510(k) devices or should they be subject to the more stringent requirements for a high-risk device or PMA, and that is a process we are moving forward towards. If we make that decision and if it is rulemaking, and that is the challenge. If we change classification and we up-classify, it is rulemaking.

Mr. MARKEY. What do you say to this woman? What can you do for the thousands of other women out there? The device is still out

on the market, so what can you say to all these tens of thousands of additional women who are being advised by their doctors right now that it is an FDA-approved technology. I mean, this is something that doesn't work and in fact it harms women. What should we say to that woman?

Dr. SHUREN. So I will tell you in the case of pelvic organ prolapse, one, we have gone out with information communications to patients. We have been working with the health care professional community.

Mr. MARKEY. This woman is a truck driver, and her physician in some town in Colorado told her it was safe. What can we say to her in terms of other women who are just in the same similarly situated predicament?

Dr. SHUREN. Again, I empathize.

Mr. MARKEY. I understand. Empathy is important, and we appreciate your empathy. But what can you say to her beyond empathy in terms of she is concerned and she is like a Paul Revere trying to warn these defective bladder meshes are coming?

Dr. GINGREY. Would the gentleman yield?

Mr. MARKEY. Sure, I would be glad to yield.

Dr. GINGREY. And I appreciate the gentleman from Massachusetts yielding to me. Of course, as he knows, I am a physician member, and I am, like Dr. Shuren, certainly tremendously empathetic to this individual's situation but meshes have been used in surgery for years and years, and whether it is an abdominal hernia situation where just a simple repair and trying to stitch things back together is not sufficient, you need that insert product to give a little strength to the repair. You know, again, in this particular situation, is it the product or could it have been an improperly placed stitch to sew the product in place? Could it have been an iatrogenic hospital-acquired infection that occasionally happens that made the procedure unsuccessful or it is really a defective product? Thank you for yielding. I just wanted to—

Mr. MARKEY. Thank you, Doctor. In this particular case, it is in fact a recurrence of a defect in the technology that had already been identified and was in the original predicate technology that the FDA did not have the ability to take off the market as another company is making the same technology with the same defect in it that was correctable but the new company did not feel it had to correct it because the FDA was still approving it. So that was where the problem originated, and thousands of women are still having it inserted into them. Is that not correct?

Dr. SHUREN. Most of the issues we are dealing with with surgical mesh are probably not a matter of replicating a problem in the predicate. Many of the things we are seeing may be issues about, are they in the right framework to begin with, are we actually getting adequate assurances in the way they are currently regulated generally that they are in fact safe and effective.

Mr. MARKEY. But you do need authority here, don't you? Don't you need stronger authority to protect women like this, or what do you say to a woman like that? You need appropriate authority here to make sure that a woman like this is not victimized and thousands of others. Don't you agree?

Dr. SHUREN. Again, in her particular case, I don't know what happened, and I know people don't want to hear "empathize" but I do. I do think the case, if we wind up making a change in surgical mesh, and again, we are looking at pelvic organ prolapse but also urinary incontinence, the challenge for us is, if we change classification, this is a slightly different issue but an important one, we go through a rulemaking process, and in those rare cases where that product based upon new evidence should move to a different classification, we have to take years to make that change. That is a challenge that we do face. We are going through questions now with metal-on-metal hips. You have raised it in terms of pre-amendment devices. Our barrier is actually in those cases statutory requirement to do rulemaking, and that makes it hard, and you want to know something? I don't know what you tell patients if you find a problem like that and you make a decision to up-classify, what you do for all that time and all those—

Mr. MARKEY. This woman's life is ruined, and the only thing I could tell her is that her now ruined life in her own words, will now pay dividends for other women who won't be facing the same thing.

Mr. PITTS. The chair thanks the gentleman.

Mr. MARKEY. I thank you, Mr. Chairman.

Mr. PITTS. We will proceed for a follow-up to Dr. Burgess.

Mr. BURGESS. I thank the chairman, and I have got some other things I want to ask, but I just feel obligated. Once again, substantial equivalence does not necessarily equate clearance, and your own information that you sent to a company that receives a substantial equivalence determination, "Please be advised the FDA's issuance of a substantial equivalence determination does not mean that the FDA has made a determination that this complies with other requirements of the Act." They are referring to the Food, Drug and Cosmetic Act. I think you have authority there. Now, this situation is perhaps a little bit more ambiguous than an implantable pacemaker. I would be happy to work with you too on this issue of implantable mesh because I do think it is an important one. As the baby boom generation ages, we are going to see a lot of demand for these type of procedures, and as Mr. Markey points out, it is important that we get it right because the problems with defects down the road can be significant.

Dr. Woodcock, let me just ask you a question. I know we visited drug shortages in these hearings, and I appreciate the work that you have done, and while I wish there were some single legislative product that would correct the defect, I am not sure that there is, and then the problem is with legislative products that we may make things worse if it leads to hoarding and that sort of activity. But it also seems like, you know, we brought specific examples in these hearings to your attention—methotrexate, doxorubicin—and things have happened then as a consequence, and I am very grateful for that. I am sure the patients are grateful. But it also makes me wonder if the problem isn't one of maybe if there were a little more flexibility or creativity on the part of the FDA that some of these shortages could be mitigated without having them become a national crisis. You provided us a long list at another hearing. Do you have someone on your staff who is looking at that? There may

be unique ways to mitigate some of these shortages and perhaps we ought to get busy about doing that rather than trying to find ideal legislation.

Dr. WOODCOCK. Well, we were working on methotrexate and doxorubicin for quite a long time and we had different solutions emerge for both of those. In every case, we are using almost every tool we have. We don't make the drugs. The manufacturers make the drugs, and we try to provide them with encouragement and flexibility and lot release, like we said, batch by batch. Even if their manufacturing isn't perfect, we can mitigate many of these things. So I think we have tools to do this. We think that additional notification may be helpful. We think the proposals by the private sector for more information sharing will be helpful. We feel that some of the proposed discussion draft legislative might have unintended consequences. For example, we have this expedited review. If we have a lot of people requesting that and we know that other companies are going to be able to come up and provide the product, because we have talked to them, then we don't want to be reviewing a lot of people or clamoring for expedited review if we feel there is not going to be a shortage and the company is in production. We think deeming compliance would be a problem, all right? Because people are either in compliance or not in compliance. If they are not in compliance with GMPs, we have flexibility and they don't have to be in full compliance to be producing these shortage drugs. They just have to be producing drugs that are of good enough quality that we feel comfortable with them going into the veins of our patients, right?

Mr. BURGESS. Right. Well, the only point I was trying to make is, it does seem like there are sometimes out there that if we just worked a little harder, we would come up with them, and I just encourage you to keep doing that.

Dr. WOODCOCK. We are working very hard.

Mr. BURGESS. But one specific instance, of course, a shortage occurs right now today at any pharmacy across the country that an asthmatic cannot walk into a pharmacy and buy an over-the-counter asthma inhaler like they used to be able to before January 1st. So there is a solution there, and that would be to allow the manufacturer of the old CFC product to sell what stock they have left. This product was not deemed to be defective. It was an EPA requirement that they stop selling, not an FDA requirement, and I appreciate the fact that you are working through this problem with getting a new over-the-counter preparation available, but as you pointed out, you have difficulty with bioequivalency, and I will also readily admit that HFA is not nearly as good a propellant as CFC, and don't blame the victim. It was not because I was holding the thing upside down. It is just not as good. But having said all of that, could you help us with the EPA if you were to write Administrator Jackson that because of the difficulties you are having with assessing bioequivalence of these new products that it would be helpful to allow the company to sell the product that it already has manufactured. We are not asking them to make a single vial. All the CFC that is going to be put into vials has already been put in. The only problem is, we are preventing asthmatics from having it accessible. Can I get your help to write a letter to Administrator

Jackson to let her know of your problem so that maybe she can help us with the problem that asthmatics are having?

Dr. WOODCOCK. We have been discussing and working with the EPA on this matter.

Mr. BURGESS. Yes, but this is something that people just frankly do not understand why one federal agency and another federal agency cannot come together on a reasonable solution. That reasonable solution is, be able to sell the product as it exists in warehouses today. Again, not one single molecule of CFC is going to be produced that has not already been produced. The hole in the ozone is not going to get one millimeter bigger because we are allowing this product to be sold. Again, the CFC has already been produced and it is already in the canisters. One day it is going to come out by some mechanism or another. I just think it would be helpful to the patients of America. We could eliminate this one drug shortage overnight if you could get some cooperation with the EPA.

Mr. PITTS. The chair thanks the gentleman. Mr. Engel for 5 minutes for questions.

Mr. ENGEL. Thank you, Mr. Chairman.

Dr. Woodcock, I just have two quick questions. I want to get back to the issue of drug shortages again because during your last appearance before the subcommittee, I mentioned my concerns about drug shortages of medications that overlap with the DEA's controlled-substance jurisdiction, and I am pleased to see in this discussion draft there are provisions for the Attorney General to increase quotas as necessary within 30 days of a request from a manufacturer. So let me ask you this. Do you believe that the majority of drug shortages in the controlled-substance category can be effectively prevented if the Attorney General addresses this request within the 30-day window or do you believe a shorter window would be necessary to ensure patient access to needed medications?

Dr. WOODCOCK. I am not familiar enough with DEA procedures to answer your question accurately. There are many causes of drug shortages, and certainly not all shortages of controlled substances may be related to DEA procedures or quotas or what have you. So I think it is a complicated issue and we would be glad to work with you.

Mr. ENGEL. OK. How about the 30 days, though? Do you think that is sufficient? It might be a little too long if someone really needs a medication.

Dr. WOODCOCK. Again, it is very difficult for me to put that into—to understand what impact 30 versus a shorter time would have on an unfolding shortage situation.

Mr. ENGEL. OK. Well, we will work with you on it.

During the last PDUFA reauthorization, I worked—this is a couple years ago—I worked with Congresswoman Blackburn and Congresswoman Giffords at that time to authorize critical path public-private partnerships, and to date, the Critical Path Institute in Arizona and the Clinical Data Interchange Standards Consortium have worked under this partnership to improve the regulatory science that FDA and industry depend on when developing and improving new pharmaceuticals and medical devices. So I am wondering if you could comment on that? It is sort of loaded question, but I want you to be on the record, because I feel strongly about

the importance of the critical path public-private partnerships and the FDA's work, so I would like you to comment on that and what role you see for these partnerships in the future.

Dr. WOODCOCK. Well, first of all, the Critical Path Institute has done a number of projects that are essential. For example, we have new biomarkers now being tested in the clinic for drug-induced renal failure, something we don't have any sensitive indicators for, and so this is a tremendous advance in regulatory science if we can get these. We have qualified them for animal studies. If we can use them in humans, that would be a tremendous advance for drug development.

As far as the clinical data standards, as we move into developing electronic health records for the public and so forth, having unified standards for how you collect data in clinical trials not only will help companies, it will help the FDA and it will help all the investigators in efficiently performing clinical trials. Right now, we have a tremendous problem of loss of clinical studies from the United States and going elsewhere, and harmonized standards within the United States for clinical data are a tremendous requirement and would really help both drug development and understanding the role of medical products and their outcomes in our population. So this type of regulatory science that is being done by the Critical Path Institute and other public-private partnerships is really building for the future, and we really endorse it.

Mr. ENGEL. Well, thank you. I couldn't agree with you more, and you gave me the answer I wanted, so thank you very much.

Mr. Chairman, I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman and yields to the ranking member for a unanimous consent request.

Mr. PALLONE. Thank you, Mr. Chairman. I just would like to make a unanimous consent request that the statement of Congresswoman Anna Eshoo as well as some questions that she is promulgating to Dr. Janet Woodcock be entered into the record.

Mr. PITTS. Without objection, so ordered.

We will make sure you get all of the questions for follow-up, if you would respond in writing.

That concludes our first panel. Thank you, Dr. Woodcock, thank you, Dr. Shuren, for your testimony and your responses. The committee will recess for 5 minutes as we change for panel number two and we will reconvene in 5 minutes.

[Recess.]

Mr. PITTS. The 5 minutes having expired, we will reconvene the subcommittee, and we now have panel number two. I would like to thank all of you for agreeing to testify before the subcommittee today. I would like to quickly introduce our expert panel.

First, Dr. David Wheadon is Senior Vice President of Scientific and Regulatory Affairs at Pharmaceutical Research and Manufacturers of America. Dr. Sara Radcliffe is Executive Vice President of Health at Biotechnology Industry Organization. Mr. David Gaugh is Vice President of Regulatory Sciences at the Generic Pharmaceutical Association. Mr. Joseph Levitt is Partner at Hogan Lovells and is testifying on behalf of Advanced Medical Technology Association. And Mr. Allan Coukell is Director of Medical Programs of Pew Health Group at the Pew Charitable Trust.

Again, thank you all for coming. We have your prepared statements. They will be entered into the record. We ask that you summarize your opening statements in 5 minutes. We are scheduled to vote in about 20 minutes. We will try to get through the presentations before having to go to the floor for the vote.

So with that, Dr. Wheadon, we will begin with you. You are recognized for 5 minutes to summarize your testimony.

STATEMENTS OF DAVID E. WHEADON, M.D., SENIOR VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA; SARA RADCLIFFE, EXECUTIVE VICE PRESIDENT OF HEALTH, BIOTECHNOLOGY INDUSTRY ORGANIZATION; DAVID GAUGH, R.PH., VICE PRESIDENT, REGULATORY SCIENCES, GENERIC PHARMACEUTICAL ASSOCIATION; JOSEPH A. LEVITT, J.D., PARTNER, HOGAN LOVELLS US LLP, ON BEHALF OF ADVANCED MEDICAL TECHNOLOGY ASSOCIATION; AND ALLAN COUKELL, DIRECTOR OF MEDICAL PROGRAMS, PEW HEALTH GROUP, THE PEW CHARITABLE TRUSTS

STATEMENT OF DAVID E. WHEADON

Dr. WHEADON. Chairman Pitts, Ranking Member Pallone and members of the subcommittee, good afternoon. I am David Wheadon, Senior Vice President, Scientific and Regulatory Affairs, at the Pharmaceutical Research and Manufacturers of America, better known as PhRMA. PhRMA appreciates this opportunity to appear before you again today in order to share our views on the 5th reauthorization of the Prescription Drug User Fee Act and on the reauthorization of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

PhRMA and its member companies strongly support the original goals of PDUFA, namely to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the agency's regulatory oversight. PDUFA has advanced public health by accelerating the availability of innovative medicines to patients while helping to ensure patient safety. PDUFA has also played a role in improving America's competitiveness around the world.

Since the passage of the original PDUFA in 1992, the United States has become the world leader in bringing new medicines to patients first, ensuring that the United States maintains a policy and regulatory environment that encourages an efficient, consistent and predictable drug review process is key to keeping America competitive in today's global economy.

The PDUFA V performance goals letter was created with an impressive inner transparency and involvement from diverse stakeholders including patients, health care providers and academia. This agreement will provide FDA with the resources and tools required for further enhancing the timeliness, completeness and efficiency of the drug review process including provisions to advance regulatory science and modernize drug development, to improve benefit-risk decision making and to further strengthen FDA's focus

on patient safety. PhRMA strongly endorses the recommendations of the PDUFA V performance goals letter and urges Congress to reauthorize this important legislation in a timely manner based on the negotiated agreement. Failure to reauthorize PDUFA in a timely fashion would have catastrophic effects on the ability of FDA to carry out its important role in bringing innovative medicines to patients.

I would like to focus for a moment on one specific aspect of PDUFA. The enhanced New Molecular Entity review model, or NME review model, will improve the review process for new molecular entity drug and biologic applications. This will be particularly significant for patients because NMEs are novel compounds that have the potential to address unmet medical needs and advance patient care. Specifically, it is anticipated that earlier and more comprehensive communication between the agency and drug sponsors as required in this enhanced review model will improve the rate of on-time first-cycle successes. The success of the new review program and of the agency's ability to achieve its drug review goals will be independently assessed in 2015 and 2017.

PDUFA V will continue to provide FDA with the necessary tools and resources that are essential to support patient safety and promote medical innovation through enhanced timeliness, completeness and efficiency of the drug review process. PhRMA encourages Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA V performance goals and to minimize the inclusion of additional provisions that may have the unintended consequences of distracting from the Act's original intent.

The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients. According to the FDA, the current pediatric exclusivity program has done more to spur research and create critical information about the use of medicines in pediatric patients than any other government initiative. Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improved pediatric medical care in the face of rising research costs.

Since its initial enactment and subsequent reauthorizations, BPCA and PREA have been subject to a sunset clause under which their provisions expire after 5 years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children, Congress should permanently reauthorize BPCA and PREA.

We would particularly like to thank Representatives Eshoo, Rogers and Markey for their work towards a bipartisan effort for a permanent reauthorization of these important pieces of legislation.

In summary, PhRMA and its member companies are committed to working closely with FDA, Congress and all stakeholders to ensure the continued success of PDUFA in bringing safe, effective and innovative medicines forward to address unmet medical needs for all patients including children. PhRMA therefore urges Congress to reauthorize PDUFA V and to permanently reauthorize BPCA and PREA in the most expeditious manner possible.

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

[The prepared statement of Dr. Wheadon follows:]

Statement



TESTIMONY OF DAVID E. WHEADON, M.D.
SENIOR VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS
PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PhRMA)
HOUSE COMMITTEE ON ENERGY AND COMMERCE, SUBCOMMITTEE ON HEALTH
HEARING ON "FDA USER FEES 2012:
HOW INNOVATION HELPS PATIENTS AND JOBS"
APRIL 18, 2012

Chairman Pitts, Ranking Member Pallone, Members of the Subcommittee, good afternoon. I am David Wheadon, Senior Vice President, Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA appreciates this opportunity to testify today and share our views on the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) and the reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

Reauthorization of the Prescription Drug User Fee Act (PDUFA-V)

PDUFA has been a great success for patients – the tens of millions of Americans who rely on innovative drugs and biologics to treat disease and to extend and improve the quality of their lives. The PDUFA user fee program has provided FDA with additional staffing and resources it needed to significantly reduce the timeframe for review of new medicines, while protecting public health by assuring the safety of these products. Furthermore, PDUFA has helped to improve America's competitiveness around the world. Since the passage of the original Prescription Drug User Fee Act in 1992, the U.S. has become the world leader in bringing new medicines to patients first.

The PDUFA-V performance goals letter is the result of extensive negotiations between the U.S. Food and Drug Administration (FDA) and the innovative biopharmaceutical industry and is intended to improve FDA's ability to conduct thorough and efficient reviews of new medicines for patients. FDA's process for negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers and academia.

PhRMA and its members, the country's leading pharmaceutical research and biotechnology companies, strongly support the original goals of PDUFA, namely - to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the Agency's regulatory oversight.

PhRMA strongly endorses the recommendations of the PDUFA-V performance goals letter. This agreement will provide FDA with the resources and tools required to further enhance the timeliness, completeness, and efficiency of the drug review process. Failure to reauthorize PDUFA in a timely manner would have catastrophic effects on the FDA's ability to carry out its important role in bringing new medicines to patients suffering from debilitating diseases.

The Role of PDUFA in Encouraging Innovation and Economic Growth. Ensuring that the U.S. maintains a policy and regulatory environment that encourages an efficient, consistent and predictable drug review process is key to keeping America competitive in today's global economy. A 2011 report by *Battelle*¹ found that the U.S. biopharmaceutical industry "is well recognized as a dynamic and innovative business sector generating high quality jobs and powering economic output and exports for the U.S. economy." According to the report, nationwide the sector supported a total of 4 million jobs in 2009, including 674,192 direct jobs. The total economic output from the sector's direct, indirect, and induced impacts was \$918 billion. Because PDUFA has injected greater consistency, transparency and predictability into the FDA's drug review process, its reauthorization is an important factor in ensuring that biopharmaceutical companies maintain this level of job creation and economic growth. Failure to reauthorize PDUFA in a timely manner would not only have an extraordinarily disruptive effect on the Agency and impede patients' access to new and innovative treatments, but such a failure would also endanger biopharmaceutical innovation.

There are a number of important new commitments in the carefully negotiated PDUFA-V performance goals letter, including provisions to make the regulatory review of new medicines more efficient and timely, to advance regulatory science and modernize drug development, to improve benefit/risk decision-making, and to further strengthen FDA's focus on patient safety.

¹ Battelle Technology Partnership Practice. The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation. July 2011. Battelle Memorial Institute. Prepared for the Pharmaceutical Research and Manufacturers of America.

Below I discuss these significant enhancements of the PDUFA-V performance goals letter.

Enhanced NME Review Program. PDUFA-V will improve the review process for new molecular entity (NME) drug and biologic applications which will be particularly significant for patients, because NMEs are novel compounds that have the potential to address unmet medical needs and advance patient care. The enhanced NME review model addresses the increasing complexity of reviewing new drug applications (NDAs) and biologic license applications (BLAs), and provides for increased communication between FDA and drug sponsors prior to and during the drug review process. A validation period will help FDA plan activities such as inspections and advisory committee meetings, and will accommodate iterative interactions between sponsors and the Agency. As a result, the NME review program is expected to improve the efficiency of the review process and reduce the overall time until new medicines become available to patients. Specifically, it is anticipated that earlier and more comprehensive communication between the Agency and drug sponsors will improve the rate of “on-time, first-cycle” successes – that is, the number of new medicines that are fully reviewed and for which definitive regulatory action is taken within the target timeframe following initial submission. The success of the new review program and of the Agency’s ability to achieve its drug review goals will be independently assessed and publicly reported in 2015 and 2017.

Advancements in Regulatory Science. Several new provisions in the PDUFA-V performance goals letter will afford FDA with appropriate staffing and resources to develop, through public input, new tools and methods to integrate emerging scientific data and techniques into the drug development and review process. These advancements in regulatory science will rely on engagement with industry, academia and other stakeholders to identify best practices so the Agency can provide appropriate guidance to stakeholders involved in drug development.

Provisions to enhance FDA’s regulatory review capabilities include:

- The use of pharmacogenomics and biomarkers to decrease drug development time by helping demonstrate therapeutic benefits more rapidly, and identifying patients who are likely to benefit from treatment, as well as those at increased risk for serious adverse events.
- Avenues for accelerating drug development for rare and orphan diseases and provide FDA with the necessary regulatory flexibility to encourage and advance research into novel treatments for patients

with significant unmet needs today.

- Standards for and validation of patient-reported outcomes and other assessment tools that may assist regulators in evaluating treatment benefits and potential risks from the patient’s point of view.
- And the evaluation of the use of meta-analyses in regulatory review and decision-making, highlighting best practice and potential limitations.

Systematic Approach to Benefit-Risk Assessment. A key provision in the PDUFA-V performance goals letter recognizes that the drug review process could be improved by a more systematic and consistent approach to benefit-risk assessment that fairly considers disease severity and unmet medical needs. During PDUFA-V, the Agency will implement a structured benefit-risk framework, and hold public meetings to assess the application of such frameworks in the regulatory environment. In addition, over the course of PDUFA-V the Agency will hold a series of public meetings with the patient advocacy community to identify disease states that – from the patient perspective – have considerable unmet needs. Development and implementation of a patient-focused, structured framework for evaluating benefits and risks of new treatments will help inform the drug development process as well as ensure that regulatory decisions are consistent, appropriately balanced, and based on best science.

Modernizing the U.S. Drug Safety System. Finally, further enhancement and modernization of the FDA drug safety system under PDUFA-V will ensure that patient safety remains paramount. The PDUFA-V performance goals letter provides for a public process to help standardize risk evaluation and mitigation strategies (REMS), with the intent to assess and reduce burden on healthcare providers and patients. Additionally, FDA will continue to evaluate the feasibility of using the Agency’s Sentinel Initiative to actively evaluate post-marketing drug safety issues.

PDUFA has advanced public health by accelerating the availability of innovative medicines to patients while helping to ensure patient safety. The PDUFA program has strengthened the scientific basis of FDA’s regulatory review process through the development and application of new tools, standards, and approaches that facilitate assessment of the safety and efficacy of innovative drugs and biologics. PDUFA-V will continue to provide FDA with the resources and tools that are essential to support patient safety and promote medical innovation through enhanced timeliness, completeness, and efficiency of the drug review process. PhRMA encourages Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA-V performance goals, and to minimize the inclusion of additional provisions that may have the unintended consequence of distracting from the Act’s original intent - to provide patients

with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the Agency's regulatory oversight.

Reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research and Equity Act (PREA)

Prior to passage of the pediatric exclusivity provisions in the Food and Drug Modernization Act (FDAMA) of 1997, there were significant disincentives for biopharmaceutical companies to conduct clinical trials for pediatric use - generally speaking, in patients under the age of 18 - for medicines developed primarily for adults. At the same time, there were concerns that many FDA-approved drugs had not been clinically tested in children. For example, at that time about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information.²

Growing recognition of the need for pediatric-specific information prompted action by Congress and the FDA. Congress responded by establishing BPCA to provide incentives to encourage manufacturers to conduct pediatric studies of medicines with the potential for use in children as part of FDAMA. The legislation included a provision that granted pharmaceutical companies an additional six-month period of exclusivity, known as pediatric exclusivity, upon the completion and submission of pediatric studies that meet the terms of a written request from FDA.

In addition to BPCA, the Pediatric Research and Equity Act (PREA) gave FDA the authority to require manufacturers to conduct pediatric studies for certain new drugs and biologics approved for use in adults where the indication for use in children would be comparable to that for adults and produce formulations appropriate for children, *e.g.* liquid or chewable tablets.

Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in BPCA and PREA in 2002, and again in 2007 as part of the Food and Drug Administration Amendments Act (FDAAA). Similarly, there are provisions in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) to provide pediatric exclusivity for biologics if the

² U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

sponsor submits pediatric studies in accordance with a written request from FDA. BPCA and PREA both sunset on September 30, 2012, unless reauthorized or made permanent.

BPCA and PREA have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients. According to the FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative.³ As of 2008, an estimated 50 to 60 percent of prescription drugs used to treat children have been studied in some part of the pediatric population.⁴ Since 1998, BPCA and PREA have resulted in 426 pediatric labeling changes⁵ and a GAO report released in May 2011 states that pediatric studies conducted in the past five years represent 16 different therapeutic areas including oncology, endocrinology, hematology, cardiovascular disease, infectious disease, and neurology.

A recent issue of the NIH's *NIH MedlinePlus* magazine notes the importance of pediatric clinical trials and cites several examples of how clinical trial knowledge has improved the lives of children. The article states that, among other examples of great progress in innovative pediatric drug development, "as a result of repeated clinical trials in children with cancer, most children who develop leukemia survive" compared to 50 years ago when "acute leukemia was almost universally fatal in young children". Additionally, clinical trials in young children "showed that surfactant - a substance that keeps air sacs in the lungs inflated - helps premature infants breathe" and with this knowledge "the lives of thousands of babies who would otherwise die of respiratory failure are saved each year".⁶

Permanent Reauthorization of BPCA and PREA is Key to Ensuring Innovation in Pediatric Research. Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improvement in pediatric medical care in the face of rising research costs. Since its initial enactment and subsequent reauthorizations, the pediatric exclusivity incentive and PREA have been subject to a "sunset clause" under which their provisions expire after five years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children over the past fifteen years, Congress should permanently reauthorize BPCA and PREA.

³ Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

⁴ FDA, "Giving Medication to Children: Q&A With Dianne Murphy, MD." June 2009.

⁵ FDA, <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf>

⁶ NIH Medline Plus, "Developing Safe and Effective Medicines for Children," Winter 2012. <
http://www.nlm.org/Program_MLP/MLP_intro.html>

Permanent reauthorization of these provisions would provide greater certainty to companies by allowing a more predictable regulatory path and would help spur increased pediatric research, a fact also highlighted in the recently released Institute of Medicine (IOM) report entitled, “Safe and Effective Medicines for Children”⁷. Pediatric product development would also benefit from updated regulatory guidance to assist both industry and FDA review staff in achieving a common understanding of the requirements under the Federal Food, Drug, and Cosmetic Act (FDCA). Because of the five-year BPCA/PREA sunset and reauthorization cycle, no such current guidance exists, since every reauthorization has brought new changes to the law. The lack of current FDA guidance creates additional challenges for sponsors involved in pediatric product development to incorporate any differences into its plans due to changes in statutory requirements. If Congress were to reauthorize BPCA and PREA permanently, it would enable the FDA to publish and maintain up-to-date regulatory guidance for companies that seek to develop pediatric treatments.

Further, making BPCA and PREA permanent would allow sponsors to build upon the existing pediatric research infrastructure and expand their capacity to conduct clinical studies. Uncertainty about whether incentives will continue could deter this vital investment. A similar pediatric incentive was successfully introduced in the European Union in 2007, and while the regulation is subject to review, the EU’s pediatric incentive is permanent. The permanent incentive in the EU has enabled the European Medicines Agency (EMA) to publish clear guidelines for industry and regulators making the process more efficient, transparent, and predictable.

Given the undisputed success of BPCA and PREA, we urge Congress to permanently reauthorize BPCA and PREA in its current form to allow pediatric research to thrive and create more options for our most vulnerable population, children. Additionally, PhRMA and its member companies are committed to working closely with FDA, and all stakeholders, to insure the continued success of PDUFA in bringing safe, effective innovative medicines forward to address unmet medical needs for all patients. PhRMA therefore urges Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA-V agreement.

Thank you for the opportunity to testify today and I welcome any questions you may have.

⁷ IOM (Institute of Medicine). 2012. *Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act*. Washington, DC: The National Academies Press.

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

STATEMENT OF SARA RADCLIFFE

Ms. RADCLIFFE. Thank you. Chairman Pitts and Ranking Member Pallone, I appreciate the opportunity to be here today. I am Sara Radcliffe, Executive Vice President for Health for the Biotechnology Industry Organization, BIO. I led BIO's engagement in the Prescription Drug User Fee Act technical discussions with the Food and Drug Administration and managed BIO's involvement in the biosimilars user fee technical discussions as well.

BIO supports quick enactment of the PDUFA V recommendations and we are supportive of the draft user fee package that the committee has released. This committee has reached strong bipartisan compromises on many issues that of critical importance to our industry. We believe that enhancements under PDUFA V will improve the drug development and review process through increased transparency and scientific dialog, advance regulatory science and strength postmarket surveillance. Most importantly, from the standpoint of young, innovative companies, our hope is that PDUFA V will provide patients and doctors with earlier access to the cures and treatments of tomorrow.

The PDUFA V legislation will reinforce FDA's review performance and get back to basics for patients. These enhancements include a New Molecular Entity review program that will lead to fewer review cycles and earlier patient to needed treatment, enhanced communication during drug development, regulatory science modernization and robust drug safety and postmarket surveillance capacities.

BIO supports FDA's ongoing implementation of a well-constructed, science-based pathway for the approval of biosimilar products. Establishing a sound BSUFA was also a priority for us. A transparent, predictable and balanced regulatory framework for the review and approval of biosimilars accompanied by reasonable performance goals and a dedicated independent funding stream will ensure that FDA can facilitate the development and evaluation of biosimilar products.

There are a number of other important provisions included in the draft that are of critical importance to BIO. Modernizing the Accelerated Approval pathway has been a top priority, and we are extremely pleased that the draft included H.R. 4132, the Faster Access to Specialized Treatments, or FAST Act, introduced by Congressmen Cliff Stearns and Ed Towns. FAST will ensure that FDA can utilize the Accelerated Approval pathway as fully and frequently as possible while maintaining FDA's safety and effectiveness standards.

The Accelerated Approval pathway has been a great success story. In certain disease areas such as cancer and HIV, the pathway has stimulated an explosion of investment in innovation and has brought immense benefit to patients. We appreciate Congress working to expand the pathway so that patients suffering from other life-threatening and rare diseases can benefit as well.

The Best Pharmaceuticals for Children Act and Pediatric Research Equity Act have greatly improved health outcomes for chil-

dren. However, the 5-year sunset periods have resulted in an uncertain regulatory environment for pediatric drug development that makes it difficult for our company and practically impossible for the FDA to issuance guidance to promote understanding of the current regulatory framework. BIO thanks Congressman Mike Rogers, Congresswoman Anna Eshoo and Congressman Ed Markey on their championship of this important issue and we support the inclusion of their legislation in the committee draft.

It is also important that FDA has access to the most knowledgeable and most qualified scientific minds to help inform key public health decisions and evaluate the safety and effectiveness of innovative new cures and treatments for patients. BIO thanks Representative Burgess and Ranking Member Pallone for their work to enhance FDA's ability to impanel highly qualified external scientific advisors while maintaining the highest levels of integrity for these proceedings.

Additionally, BIO looks forward to continuing to work with the committee to enhance oversight over the upstream supply chain for pharmaceutical ingredients and modernizing the downstream domestic supply chain for finished pharmaceutical products. BIO supports the establishment of strong, uniform national standards for serialization and tracing systems rather than relying on the emerging patchwork of individual State mandates. In this case, BIO believes that Congress should enact laws governing drug product serialization and traceability systems that regulators can leverage to hold supply chain member accountable for ensuring that legitimate product reaches the patient. A national system using existing and proven technologies would best protect supply chain integrity and patient safety.

Thank you again for the opportunity to testify. We look forward to working with all of you to ensure that the user fee package is quickly enacted.

[The prepared statement of Ms. Radcliffe follows:]

**TESTIMONY OF SARA RADCLIFFE
EXECUTIVE VICE PRESIDENT, HEALTH
BIOTECHNOLOGY INDUSTRY ORGANIZATION (BIO)
HOUSE COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON HEALTH
HEARING ON "FDA USER FEES 2012: HOW INNOVATION HELPS
PATIENTS AND JOBS."**

APRIL 18, 2012

Chairman Upton and Pitts, Ranking Member Waxman and Pallone, Members of the Committee, it is my privilege to provide testimony before you today. My name is Sara Radcliffe and I am Executive Vice President for Health for the Biotechnology Industry Organization (BIO). In that role, I led BIO's engagement in the Prescription Drug User Fee Act (PDUFA) technical discussions with the Food and Drug Administration (FDA) and managed BIO's involvement in the biosimilars user fee (BsUFA) technical discussions.

BIO represents over 1,100 members involved in the research and development of innovative healthcare, agricultural, industrial, and environmental technologies. The U.S. biotechnology industry is poised to be a major driver in an innovation-driven economy. Biotechnology offers 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.

PDUFA V: GETTING BACK TO BASICS FOR PATIENTS

BIO supports quick enactment of the PDUFA V recommendations as we believe they can enhance the drug development and review process through increased transparency and scientific dialogue, advance regulatory science, and strengthen post-market surveillance. Most

importantly, from the standpoint of young, innovative companies, our hope is that PDUFA V will provide patients and doctors with earlier access to breakthrough therapies.

When we began the process of organizing for our discussions of PDUFA V, we in the industry started with a simple set of principles that could provide the foundation for our discussions with FDA and other stakeholders. These were that a science-based, transparent, and well-managed review process that appropriately balances benefits and risks can enhance public trust and increase patient access to new medicines.

With these principles in mind, industry and FDA agreed upon a set of enhancements under PDUFA V that seek to reinforce FDA's review performance and get back-to-basics for patients. These proposals also have been informed by an unprecedented level of public input through workshops, meetings, and stakeholder outreach, which further strengthened the technical agreement. These enhancements include:

- **New Molecular Entity (NME) Review Program**: Historically, nearly 80% of all NME applications submitted to FDA are ultimately approved, but fewer than half are approved on the first submissionⁱ. Sponsors and FDA can and must do better for patients. By strengthening scientific dialogue and transparency between FDA and Sponsors under the proposed review program for novel drugs and biologics, we can minimize the potential review issues that can delay patient access to needed treatments. Increased FDA-Sponsor scientific dialogue and transparency, such as a mid-cycle communication, exchange of discipline review letters and advisory committee information, and a significant new late-cycle meeting, will help to identify and resolve issues earlier in the review. This represents a significant paradigm shift in FDA's review process while

maintaining FDA's high standards for safety and efficacy. An additional two-month validation period during the review period will help to ensure FDA has all the information it needs at the beginning of the process to perform a complete review. Finally, a robust third-party evaluation will provide data on whether we have been successful in this program of leading to fewer review cycles, shorter approval times, and earlier patient access to needed treatment.

- **Enhanced Communication during Drug Development:** To help advance American innovation and promote the development of the next generation of modern medicines, FDA has also committed to a philosophy under PDUFA V that timely, interactive communication with biotechnology and life science companies during drug development is a core Agency activity. The scientific method does not operate in a vacuum, and it is critical to promote interactive, scientist-to-scientist communication between FDA and Sponsors. In the course of drug development, Sponsors sometimes have simple or clarifying questions, the responses to which could have a significant impact on the development program, but which are not extensive enough to warrant formal meetings. To obtain timely responses to such questions, Sponsors currently often have to engage in a lengthy exchange of multiple formal letters with FDA, which is an inefficient and cumbersome use of both FDA's and the Sponsor's time. For small biotechnology companies reliant on limited venture capital, these delays can create significant impediments to development programs.
- **Modernizing Regulatory Science:** Additionally, the PDUFA V agreement makes new resources available to modernize regulatory science, for example, in the areas of personalized medicine and rare disease drug research. Modern approaches to drug

development and evaluation, such as through the application of new tools for rare disease drug development, flexibility with regard to creative study designs and new endpoints, greater utilization of biomarkers and patient reported outcome tools will introduce new efficiencies in the drug development enterprise and provide FDA with additional tools to evaluate the benefits and risks of pharmaceutical products. These proposals will also integrate more structured and systematic approaches to assessing benefits and risks of therapies, and allow FDA to conduct outreach to patients and hold workshops to understand better patient perspectives on disease severity and unmet medical need.

- **Robust Drug Safety and Post-Market Surveillance Capacity:** PDUFA V continues industry's commitment to a lifecycle approach to product evaluation by strengthening FDA's post-market surveillance and benefit/risk management capacity. Earlier discussion of risk management strategies, standardized approaches to REMS, and further validation of the Sentinel Network will promote patient confidence in drug and biologics.

Under the PDUFA V agreement, industry has reinforced its commitment to a well-funded drug and biologics program that supports sound, science-based regulation consistent with FDA's public health mission. However, user fees are intended to support limited FDA activities around the drug review process and were never intended to supplant a sound base of appropriations. User fees currently account for nearly two-thirds of the cost of human drug review. We urge Congress to support FDA's mission and fund the Agency at the Administration's FY12 requested levels.

BIO SUPPORTS PASSAGE OF THE BIOSIMILARS USER FEE PROGRAM

BIO supports FDA's ongoing implementation of a well-constructed, science-based pathway for the approval of biosimilar products. A transparent, predictable, and balanced regulatory framework for the review and approval of biosimilars, accompanied by reasonable performance goals and a dedicated, independent funding stream, will ensure that FDA can facilitate the development and evaluation of biosimilars products.

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

- Ensuring Patient Safety
- Recognizing Scientific Differences Between Drugs and Biologics
- Maintaining the Physician-Patient Relationship
- Preserving Incentives for Innovation
- Ensuring Transparent Statutory and Regulatory Processes
- Continuing to Prioritize FDA Review and Approval of New Therapies and Cures

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

FAST PROVIDES CRITICAL REFORMS TO ACCELERATED APPROVAL

The FDA's Accelerated Approval pathway 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."ⁱⁱ

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, 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 in innovation in those 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.ⁱⁱⁱ BIO supports H.R. 4132, the Faster Access to Specialized Treatments (FAST) Act, introduced by Congressmen Cliff Stearns and Ed Towns, which would ensure that FDA could 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.

PEDIATRIC DRUG DEVELOPMENT

The Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) have been remarkably successful in ensuring that the medications used in children are tested and labeled appropriately for their use. BPCA and PREA have generated a wealth of pediatric drug information for physicians and parents, contributing to improved health outcomes for pediatric patients. Working in tandem, BPCA and PREA have resulted in nearly 425 pediatric labeling changes since 1998, according to the FDA. Congress should recognize the success of these programs and:

- Reauthorize the existing framework and incentive for ongoing pediatric research, and
- Make the programs permanent by eliminating their sunset provisions.

The five year sunset periods for BPCA and PREA result in an uncertain regulatory environment for pediatric drug development. Since the average pediatric clinical research program spans 6 years, most clinical programs will span two reauthorization periods in which the ground-rules for pediatric research are subject to change. This uncertainty makes it difficult for companies to invest in infrastructure to support development of products for children, and practically impossible for the FDA to issue guidance to promote understanding of the current regulatory framework.

Since their enactment, BPCA and PREA, working together, have been widely acknowledged as effective in promoting pediatric drug research. There is no logical reason to continue to allow such important legislation to sunset, as the ambiguity associated with this situation has the potential for limiting or endangering the pediatric research infrastructure that companies have been endeavoring to build and expand. BIO supports H.R 4274, the BPCA and PREA Reauthorization Act and thanks Congressman Mike Rogers, Congresswoman Anna Eshoo, Congressman Ed Markey and others on their championship of this important issue.

REFORM OF ADVISORY COMMITTEE CONFLICT OF INTEREST POLICIES

As a pre-eminent science-based regulatory agency, it is critical that FDA have access to the most knowledgeable and most qualified scientific minds to help inform key public health decisions and evaluate the safety and effectiveness of innovative new cures and treatments for patients. BIO thanks Representative Burgess for his work on this issue and for introducing legislation that will enhance FDA's ability to empanel highly-qualified external scientific advisors, while maintaining the highest levels of integrity for these proceedings.

In recent years, arbitrary limits and unnecessarily restrictive interpretations of conflict of interest rules have created barriers that have prevented FDA from consistently recruiting highly qualified scientific advisors. Consequently, advisory committee vacancies are at an all-time high, the quality of the scientific discourse on such panels has suffered, and FDA has at times had to rely on scientific advice from panel members lacking relevant expertise, particularly with respect to rare diseases and cutting-edge technologies where the pool of available experts can be quite small.

BIO believes that FDA should have greater flexibility and discretion to select the most appropriate advisors, consistent with the rules that apply to other federal agencies. Such changes will help to ensure that FDA decisions are informed by the best available scientific experts and in the best interest of patients.

FDA MISSION STATEMENT

FDA's mission, as amended by the Food and Drug Administration Modernization Act of 1997 and set forth in section 903 of the Federal Food, Drug, and Cosmetic Act (FFDCA), is to promote and protect the public health. However, the FDA mission statement does not reflect the Agency's critical role in incorporating modern scientific advances into review practices to ensure that innovative treatments and therapies are made available to the patients who need them.

The pathway for such long-sought health technology advances as personalized medicine, health applications of nanotechnology, and other cutting-edge developments to reach patients and to improve healthcare in the United States goes through FDA. The Agency has a critical role in facilitating healthcare innovation, but this fact is not formally and forcefully recognized in FDA's legislative mandate. BIO applauds Congressman Mike Rogers for introducing legislation and advancing a dialogue on updating the FDA's mission for the 21st century.

SUPPLY CHAIN INTEGRITY & ADOPTION OF A NATIONAL PHARMACEUTICAL TRACEABILITY SYSTEM

Due to the nature of the United States' closed and highly regulated pharmaceutical supply chain, American patients have high confidence in the integrity of the drugs and biologics they are prescribed. BIO member companies believe the quality and safety of their products is their responsibility to the patients they serve, and is their first priority. BIO supports the initiatives

that FDA has already implemented to expand the Agency's global presence through foreign offices; expand the foreign inspectorate and part of a risk-based inspectional strategy; and modernize registration and facility tracking systems and information technology infrastructure.

This Committee has also been examining granting the Agency several new regulatory authorities to further secure the supply chain and BIO looks forward to working with the Committee to further strengthen FDA's import programs and oversight. BIO is supportive of well crafted proposals to increase penalties for criminal counterfeiters and adulterers, provide FDA with authority to detain or destroy known counterfeits at our ports, modernize FDA's facility registration and tracking systems, and better leverage the resources of established international regulatory authorities through joint inspections.

In addition to enhancing oversight over the "upstream" supply chain for pharmaceutical ingredients, it is critical to make enhancements to the "downstream" domestic supply chain for finished pharmaceutical products. BIO supports the establishment of strong, uniform, national standards for serialization and tracing systems, rather than relying on the emerging patchwork of individual state mandates. In this case, BIO believes that the Congress should enact laws governing drug product serialization and traceability systems that regulators can leverage to hold supply chain members accountable for ensuring that legitimate product reaches the patient. A national system using existing and proven technologies would best protect supply chain integrity and patient safety.

Specifically, this approach would standardize efforts nationwide and provide immediate measures to increase supply chain security. Such an approach would enable the identification and adoption of a consensus standard for a traceability system and establish the foundational

building blocks and scalable infrastructure to facilitate additional system advancements. Such a system should be sufficiently flexible to allow the end-state to reflect the realization of the project's goal—facilitating the identification, and preventing the introduction, of counterfeit, diverted, substandard, adulterated, misbranded or expired drugs from the supply chain and improving the efficiency and effectiveness of recalls.

CONCLUSION

Thank you for the opportunity to offer BIO's support for the "UFA" Package. We believe that these are common sense recommendations that will help advance innovative new cures for patients. We call on Congress to fully support FDA's appropriated budget and to pass PDUFA V as expeditiously as possible. I would be pleased to answer any questions from the committee.

ⁱ FY10 PDUFA Performance Report, p.4,
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf>

ⁱⁱ 21 C.F.R. § 314.500; 21 C.F.R. § 601.40

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

Mr. PITTS. The chair thanks the gentlelady.

Mr. Gaugh, you are recognized for 5 minutes for an opening statement.

STATEMENT OF DAVID GAUGH

Mr. GAUGH. Good afternoon, Chairman Pitts, Ranking Member Pallone and members of the subcommittee. I am David Gaugh, Vice President of Regulatory Science for the Generic Pharmaceutical Association and a Licensed Pharmacist. GPhA represents the manufacturers and distributors of finished dose pharmaceuticals and bulk pharmaceutical chemicals.

Generic pharmaceuticals account for 80 percent of all prescription drugs dispensed in the United States but consume just 27 percent of the total drug spending for prescription medicines. Today's generic industry is one marked by diverse, innovative companies who have grown to become global leaders in providing equivalent medicines. At the same time, generic competition continues to play a vital role in driving pharmaceutical innovation. This growth in the generic industry has led to the creation of tens of thousands of new American jobs and dozens of States across the country. It has also served to underscore the critically important role of the Food and Drug Administration. However, the administration remains underfunded and responsibility of ensuring access to safe and affordable medicines is one that is shared with the rest of the entire pharmaceutical industry, not just the FDA. That is why the generic industry has stepped up to help provide the FDA with additional resources to address the ongoing challenges caused by an increasing global drug supply chain, the increase in the agency's workload and the regulation of complex technologies.

Currently, more than 2,700 generic drug applications are awaiting approval from the FDA's Office of Generic Drugs, and the average approval time for an application is now stretching beyond 30 months, more than five times longer than the statutory six-month review time that was called for in Hatch-Waxman. Unfortunately, this backlog keeps safe, low-cost generic drugs off the market and reduces competition that may drive prices down even further.

The proposed Generic Drug User Fee Act, or GDUFA, that we are discussing today will help alleviate this backlog and expedite consumer access to these generic drugs. GPhA also recognizes, however, that while providing early access to effective medicines is critical and is a key aim of the other user fee programs, an equally important pillar of FDA and industry is to ensure drug safety. That is why GDUFA takes the unprecedented step of holding all players contributing to the U.S. generic drug system both foreign and domestic to the same inspection standards and enhances FDA's ability to identify and require the registration of active pharmaceutical ingredients and finished fill dosage for manufacturers involved in each generic drug product that is sold in the United States. It is paramount that we work to shape the future of our country's generic drug industry. We also work to bring the FDA into the 21st century and ensure that the agency's authorities to achieve its mission in this global age are up to date.

This is further exemplified by the other fee program we will discuss today, which is for generic biologic drugs or biosimilars. Bio-

logic medicines are often the only lifesaving treatment for many of the more severe diseases encountered in patients today. In many respects, they represent the future of medicine. However, their price tag can keep these products out of the reach of many patients.

During the biosimilar user fee negotiations, GPhA expressed its support for the user fee funding to provide FDA with the adequate resources to apply consistent regulatory standards to all biologics and review new applications as they are filed. Both industry and patients will benefit from this user fee program by gaining a higher degree of certainty in the timeliness of applications and their reviews. We applaud the FDA for recognizing the importance of the biosimilars and the need to apply state-of-the-art science in an agency activity governing the review and approval of these very important drugs.

Now let me turn to drug shortages. The generic pharmaceutical industry has spearheaded the development of an unprecedented multi-stakeholder private sector collaboration which we believe will accelerate the recovery of certain critical drugs in short supply to the patients in need. This solution, which has been labeled the Accelerated Recovery Initiative, will play a crucial role in assisting the FDA with a more accurate, timely and comprehensive review of current potential drug shortages and in establishing practices to lessen or even eliminate in some cases current shortages.

Finally, we urge the inclusion in the user fee legislation of a proposal introduced by Ranking Member Pallone and Representative Guthrie, H.R. 4332, the Generic Drug Application Review Fairness Act, which will ensure that generic drug manufacturers are not unfairly penalized for delays in the drug application approval process.

In conclusion, Mr. Chairman, this is truly an historic time for GPhA. Nothing is more important to our industry than ensuring patients have access to lifesaving generic medications they require and these historic agreements will provide the critical step towards accomplishing that goal. Thank you.

[The prepared statement of Mr. Gaugh follows:]

**SUMMARY OF THE GENERIC PHARMACEUTICAL ASSOCIATION TESTIMONY
BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH
UNITED STATES HOUSE OF REPRESENTATIVES – APRIL 18, 2012
“FDA USER FEES 2012: HOW INNOVATION HELPS PATIENTS AND JOBS”**

I am David Gaugh, Vice President for Regulatory Sciences at the Generic Pharmaceutical Association and a licensed pharmacist. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals and suppliers of other goods and services to the generic industry. Generic pharmaceuticals fill 80 percent of the prescriptions dispensed in the U.S. but consume just 27 percent of the total drug spending.

Today’s generic industry is one marked by diverse, innovative companies, who have grown to become global leaders both in providing equivalent medicines and pioneering new treatment options for patients. Generic competition also continues to play a vital role in driving pharmaceutical innovation. This growth in the generic industry has led to the creation of tens of thousands of new jobs across the country. We urge the Committee to approve Generic Drug User Fee Act (GDUFA) and Biosimilar User Fee Act (BSUFA) as negotiated and in a timely manner, so that patients, the FDA, and generic manufacturers can begin to see the many benefits of these agreements.

Landmark User Fee Programs Will Provide Additional Resources

Through the negotiation of GDUFA, the generic industry has stepped up to help provide the FDA with much-needed additional resources. GDUFA will help ensure U.S. drug safety, establish a more level playing field among the U.S. pharmaceutical supply chain, and make certain that Americans receive timely access to safe, effective and affordable generic drugs. Currently, more than 2,700 generic drug applications, or Abbreviated New Drug Applications (ANDAs), are awaiting approval from the FDA’s Office of Generic Drugs (OGD), and the average approval time for an application is now stretching beyond 30 months. GDUFA’s performance goals call for FDA to complete, by the end of year five, the review of 90 percent of all ANDAs that are pending on October 1, 2012 — effectively eliminating the current application backlog. By the end of the program’s fifth year, GDUFA also calls on the FDA to review 90 percent of ANDAs within 10 months after they are submitted — almost two years faster than today’s average review time. GDUFA also takes the unprecedented step of holding all players contributing to the U.S. generic drug system, foreign or domestic, to the same inspection standards, and enhances FDA’s ability to identify and require the registration of API and finished dosage form manufacturers involved in each generic drug sold in the U.S.

Biosimilar User Fee Act

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

Additional Measures are needed to Ensure Access to Affordable Medicines

Drug Shortages – GPhA supports the proactive reporting and expedited review measures in the previously released discussion draft.

Forfeiture – GPhA urges the inclusion of the forfeiture proposal introduced by Rep. Pallone and Rep. Guthrie, the Generic Drug Application Review Fairness Act of 2012.

Supply Chain Security – GPhA supports a risk-based model for foreign inspections and urges the inclusion of the RxTEC drug tracking model outlined by the Pharmaceutical Distribution Security Alliance (PDSA)

Antibiotics - GPhA supports appropriate efforts to increase incentives to develop new novel antibiotics but has concerns regarding the increased filing moratorium in the previously released draft.



TESTIMONY OF DAVID R. GAUGH, R.PH.

VICE PRESIDENT FOR REGULATORY SCIENCES

GENERIC PHARMACEUTICAL ASSOCIATION

**FDA USER FEES 2012: HOW INNOVATION HELPS PATIENTS
AND JOBS**

BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

APRIL 18, 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 your subcommittee on this very timely and important subject.

I am David Gaugh, Vice President for Regulatory Sciences at the Generic Pharmaceutical Association and a licensed pharmacist. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, bulk pharmaceutical chemicals, and the 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 consume just 27 percent of the total drug spending for prescription medicines.

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

Prior to joining GPhA, I was Vice President and General Manager for Bedford Laboratories, the generic injectable division of Ben Venue Laboratories, I have also served as Senior Director, Pharmacy Contracting and Marketing, for VHA/Novation, one of the largest Group Purchasing Organizations in the U.S., and was System Director of Pharmacy for a regional referral tertiary-care healthcare system in the Midwest.

Introduction

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

Today's generic industry is one marked by diverse, innovative companies, who have grown to become global leaders not only in providing equivalent medicines, but in pioneering new treatment options for patients. At the same time, generic competition continues to play a vital role in driving pharmaceutical innovation. New life saving medicines can only help patients if they have access to them, and this is made possible through the savings generics create both directly and indirectly by bringing down the total drug costs for every household.

Since the enactment of the Hatch-Waxman Act, which created the modern day generic industry, there has been a multiple-fold increase in the innovation of new drugs — including the cholesterol drugs Lipitor and Zocor, antidepressants Prozac and Paxil, and antiulcerants Prilosec and Nexium, among others — while at the same time an

increased use in generic drugs. By creating a fair balance between innovation of new medicines and accessibility to lower cost generic medicines, the legislation established a win-win-win system for providers, payers and consumers.

This dynamic will only heighten as the industry moves toward the development of new, complex technologies such as generic versions of biologic drugs, or biosimilars. As the Federal Trade Commission (FTC) concluded in its report "Follow-On Biologic Drug Competition", market competition from biosimilars actually will spur biologic innovation and the introduction of new medicines.

This growth in the generic industry has led to the creation of tens of thousands of new American jobs in dozens of states across the country. It has also served to underscore the critically important role of the Food and Drug Administration (FDA). As I will highlight, the level of cooperation between industry and the FDA has never been greater. The two historic user fee agreements we are discussing today represent only a small measure of our ongoing collaboration. It is our hope that this collaboration will continue and extend throughout all of our interactions with the agency.

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

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

Throughout much of last year, GPhA and our member companies worked closely with the FDA to negotiate a generic drug user fee program designed to help the agency obtain additional resources to ensure all participants in the U.S. generic drug system, whether U.S.- based or foreign, comply with all of our country's strict quality standards. Most importantly, the program will make certain that all Americans receive timely access to safe, effective and affordable generic drugs, and will provide a level playing field for U.S. and foreign manufacturers.

Landmark User Fee Programs Will Provide Additional Resources

Currently, more than 2,700 generic drug applications are awaiting approval from the FDA's Office of Generic Drugs (OGD), and the average approval time for an application is now stretching beyond 30 months, five times longer than the statutory six-month review time called for by Hatch-Waxman. Unfortunately, this backlog keeps safe, low-cost generic drugs off the market and reduces competition that may drive drug prices down further.

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

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

Splitting the fees in this manner will provide the FDA with a predictable source of annual income, as the number of facilities manufacturing generic drugs on a yearly basis provides a more consistent figure than the number of generic drug applications submitted. Any finished dose or active pharmaceutical ingredient manufacturing facility that is referenced or listed in a generic drug application — commonly referred to as an Abbreviated New Drug Application, or ANDA — will pay a facility fee under GDUFA.

The new user fee program will also establish performance goals for the FDA. As part of these goals, GDUFA calls for the agency to complete, by the end of year five, the review of 90 percent of all generic drug applications that are pending on October 1,

2012 — the proposed start date for the program. By achieving this goal, the GDUFA agreement will effectively eliminate the current application backlog.

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

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

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

GPhA believes that the FDCA should be amended to ensure that all facilities, foreign and domestic, are held to the same inspection frequency and prioritized on a risk basis.

This will improve quality, consistency and availability within the drug supply chain and create a level playing field, allowing U.S. pharmaceutical manufacturers to be more competitive. It will also benefit foreign manufacturers, who are likewise disadvantaged through delayed approval times, as a recent inspection history is required for new product approval.

These important updates to the law will result not only in a safer drug supply with consistent oversight for all players in the U.S., but will also help reduce approval times of new drugs undergoing FDA review and help expedite the availability of new medicine, as all facilities will be subject to routine FDA inspection.

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

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

That is why GDUFA takes the unprecedented step of holding all players contributing to the U.S. generic drug system, foreign or domestic, to the same inspection standards,

and enhances FDA's ability to identify and require the registration of active pharmaceutical ingredient and finished dosage form manufacturers involved in each generic drug product sold in the U.S. The program will significantly improve the resources the FDA has to do this important work, ensuring that it can be done with increasing speed, but without any sacrifice to today's high quality standards.

To that end, a critically important metric of the GDUFA program is that FDA will conduct risk-adjusted biennial current Good Manufacturing Practice, or cGMP, surveillance inspections of generic finished-dose and API manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

Achieving this inspection parity will provide significant value to industry participants, as the majority of outstanding inspections delaying ANDA approvals are associated with foreign facilities. These applications are currently disadvantaged by having to wait for an inspection before approval.

Further, the disparity in the degree of oversight experienced by domestic versus foreign facilities creates an uneven playing field between those that are receiving regular GMP inspections and those that are not. The GDUFA program will help ensure that any noncompliant players within the drug supply chain, wherever they are based, are identified in order to ensure the safety of drugs and protect the reputation of our industry around the world.

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

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

It is paramount that, as we work to shape the future of our country's generic drug industry, we also work to bring the FDA into the 21st century and ensure that the agency's authorities to achieve its mission in this global age are up to date.

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

Biosimilar User Fee Act

Biologic medicines are often the only lifesaving treatments for many of the most severe diseases encountered by patients today. In many respects, they represent the future of

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

With the FDA still working to determine the process by which these products will be approved, GPhA continues to stress the importance of creating a workable regulatory mechanism that does not serve as a barrier to competition, but rather ensures the robust competition needed to lower costs and spur future innovation. If such a system is not put in place, it is our fear that the exponential growth of biologics over the next 10 to 20 years, without adequate generic alternatives, could bankrupt our health care system and the national economy. Moreover, the lack of lower-cost generic biologics will keep vital treatments away from the patients who need them most.

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

During the biosimilar user fee negotiations, GPhA expressed its support for user fee funding to provide FDA with adequate resources to apply consistent regulatory standards to all biologics, and review new applications as they are filed. Both industry

and patients will benefit from this user fee program by gaining a higher degree of certainty in the timeliness of application reviews.

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

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

Additional Measures are needed to Ensure Access to Affordable Medicines

It is important to emphasize that the funding provided by both of these user agreements is in addition to, not a substitute for, Congressional appropriations. And while the programs provide an excellent framework for industry to help support the growing global needs of FDA and speed the entry of generic drugs to market, they do not completely solve the problem. With this in mind, we urge the Committee to address additional

areas — outside the scope of the user fee agreements — that would further increase access to safe and effective generic medicines.

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

The Committee's previously released discussion draft of the user fee legislation contains a proposal to formalize the process for proactively reporting drug shortages to the FDA — as many generic manufacturers now do voluntarily — and allow the FDA to expedite regulatory reviews. We believe this proposal would enable both the agency and industry to mitigate the damage a shortage can cause. We also applaud the inclusion in the discussion draft of a provision to expedite the review of major manufacturing changes in order to prevent or alleviate a drug shortage.

In conjunction with these efforts, the generic pharmaceutical industry is spearheading the development of an unprecedented multi-stakeholder collaboration, which we believe will accelerate the recovery of certain critical drugs in short supply to patients in need.

This solution, which we have labeled the Accelerated Recovery Initiative (ARI), is designed to provide a more accurate, timely and comprehensive view of critical drugs in drug shortage situation, provide greater visibility to potential shortages of these critical drugs and establish practices that allow for potential, voluntary production adjustments to lessen or eliminate the impact of a current shortage.

The ARI is predicated on voluntary communication between an Independent Third Party and stakeholders involved in the manufacturing and distribution of generic injectable medications currently in shortage. It is designed to use real-time supply and distribution information to give the FDA a better understanding of current conditions and expand the supply of critical medications.

This voluntary initiative will take place in conjunction with the excellent work currently being done by the FDA and members of Congress. The type of information gathered and disseminated will increase early visibility and communication between the FDA and industry relating to current and potential drug shortages.

We also urge the inclusion in the user fee legislation of a proposal introduced by Ranking Member Pallone and Representative Guthrie, H.R. 4332, the Generic Drug Application Review Fairness Act. As I mentioned earlier, the average approval time for a generic drug application is now stretching beyond 30 months, five times longer than the statutory six-month review time called for by the Hatch-Waxman Act. While GDUFA will help to lower this approval time to 10 months over the next five years, in the short

term this delay is causing certain generic manufacturers to forfeit the 180-days of market exclusivity period they would gain by successfully challenging a brand drug's patent.

This is happening because, under a provision included in the Medicare Modernization Act (MMA) of 2003, a first filer of a generic drug application must forfeit its 180-day exclusivity if it does not receive a tentative approval from the FDA within 30-months of the date its application is received. The intent of the provision was to encourage first filers to submit quality applications. If the application was not sufficiently complete to be eligible for approval upon review, it would have the threat of losing the 180-days of exclusivity.

When Congress passed MMA, the average review and approval time for an ANDA was 16 months. FDA median review and approval time of ANDAs, however, has slowly increased since 2003 and is now approximately 30 months. This unprecedented increase in approval time has caused several first filers to forfeit the 180-days of exclusivity, which was clearly not the intent of Congress. The proposed solution provides temporary relief from this unintended consequence by temporarily increasing the 30-month period to reflect the increase in median ANDA approval time in 2012. As GDUFA goes into effect, the average approval time for ANDAs will eventually be reduced. The proposal is therefore tied to the GDUFA timeline and will sunset at the end of 2017. Additionally, this relief would be available on a prospective basis only and would only apply to those first-to-file applications that have not hit their 30 months from

filing date at the time of enactment. By providing this temporary relief, the legislation will ensure that generic manufacturers can continue to challenge patents and bring generic drugs to the market sooner.

As this user fee legislation moves forward, GPhA also respectfully urges the Committee to consider including a measure to ensure the security of the U.S. pharmaceutical supply chain.

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

GPhA further supports a “risk-based” model for inspections that follows the model established by GDUFA. This model prioritizes inspections according to an establishment’s inspection, safety and compliance track record and whether an establishment is associated with ANDAs that are otherwise approvable, or eligible for tentative approval, except for an outstanding inspection. Establishments associated with ANDAs that have not been inspected previously, as well as facilities in need of a recent inspection history, also would gain priority.

This system would ensure that questionable or problematic facilities receive a comprehensive review and evaluation sooner, rather than later, or not at all as can be the case under the current system. Facilities with strong records of compliance and

positive inspections would be placed further down on the inspection schedule, unless awaiting an inspection for an application approval, allowing the agency to prioritize its immediate attention on facilities that have never had an inspection or that have a history of compliance issues.

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

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

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

Finally, I would like to note briefly our concerns with the Committee's proposal in the previously released discussion draft to incentivize new antibiotic development.

GPhA supports appropriate efforts to increase incentives to develop new novel antibiotics. Market exclusivity is a powerful tool, however, that Congress should judiciously use as an incentive to spur the development of new products. An increase in market exclusivity for specific classes of drugs is a slippery slope and prioritizes certain medical conditions over others.

Moreover, an increase in market exclusivity for certain classes of drugs could have the unintended consequence of pharmaceutical manufacturers overly focusing efforts on those classes of drugs that have larger market exclusivity periods at the expense of developing new cures for other diseases that have shorter market exclusivity periods.

GPhA has always been supportive of ensuring that innovator companies receive an appropriate amount of time to recoup their investment into research and development. The 10 years of market exclusivity that this bill affords accomplishes this balance. However, we must also be mindful of the public health aspect of antibiotics. Thus, it is important that Congress strike a delicate balance between affording market exclusivity to manufacturers and providing patients timely access to low-cost generic versions of these products. Increasing the filing moratorium to nine years, which, due to an

automatic 30-month stay and the likely six months of exclusivity for pediatric testing, would represent a de facto 12 years of market exclusivity, overlooks this balance.

Additionally, Hatch-Waxman, the Orphan Drug Act, and the Biologics Price Competition and Innovation Act all have four-year filing moratoriums. Increasing the filing moratorium for novel antibiotics to nine years would create a new and separate filing standard solely for this specific class of drugs.

Conclusion

In conclusion, Mr. Chairman, this truly is an historic time for GPhA. The user fee proposals are the culmination of months of negotiations between FDA and industry, and the final product as transmitted to Congress represents a careful balance among all the stakeholders involved. We respectfully urge the Committee to approve GDUFA and BSUFA as negotiated by FDA and industry, without any changes to the underlying agreements. It is also vital that the agreements be approved in a timely manner so that patients, the FDA, and generic manufacturers can begin to see the many benefits of these agreements. Nothing is more important to our industry than ensuring patients have access to the lifesaving generic medications they require, and these historic agreements provide a critical step toward accomplishing this goal. Thank you and I would be happy to address any questions you may have.

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

STATEMENT OF JOSEPH A. LEVITT

Mr. LEVITT. Thank you. Chairman Pitts, Ranking Member Pallone and members of the committee, my name is Joe Levitt. I am a partner in the law firm of Hogan Lovells, and I am here today on behalf of AdvaMed, MDMA and MITA, the three trade associations who participated in the MDUFA negotiations with the FDA. I was on that negotiating team throughout that process, and I am pleased to be testifying with you here today. I also spent 25 year at the FDA and for 6½ of those years during the 1990s I held the senior position in FDA's Medical Device Center.

As many of you know, the medical technology industry has been a true success story for patients and for the U.S. economy. Our industry truly leads the world but our leadership is slipping. One key reason, perhaps the most important reason, is the decline we have seen in FDA efficiency, consistency and predictability in recent years. To their credit, the FDA leadership has recognized the need to vigorously address the issues affecting the device center. The new user fee agreement has the potential to be a significant additional step in the right direction. It is good for industry, it is good for FDA, and most of all, it is good for American patients.

The user fee agreement builds the conditions for success in a number of major ways. First, for the first time ever, this user fee agreement establishes average total time goals for FDA review. Our previous agreements had set goals only for terms of the FDA clock but what matters most to industry and to patients is the actual calendar, the time from beginning of submission to final FDA decision. By setting in place this new goal, efforts will be focused on the metric that truly matters.

Second, the agreement also establishes improved goals for time on the FDA clock. These goals are a key management tool for the agency and they work in concert with the total time goal to produce better performance than either could achieve alone.

Third, the agreement includes new procedures that we anticipate will improve the review process. These include before the review actually begins meaningful presubmission interactions between FDA and companies to be sure everybody is on the same wavelength going in, during the review process a mandatory mid-course substantive interaction between FDA and the company midway through the process to check in and be sure we are all on the right wavelength there, and finally at the tail end, a new procedure that we call "no submission left behind" so that if FDA time target is missed, that submission does not fall off the radar screen.

Fourth, the agreement provides for greater accountability. Under the agreement, there will be quarterly and annual reporting on a variety of key metrics that both industry and FDA agree are important. In addition, the agreement provides an analysis of FDA's management of the review process by an independent consulting organization coupled with FDA corrective action plan to address opportunities for improvements. We see this as being critical. It is a way to bring fresh eyes to the issues and work constructively towards meaningful process improvements.

Finally, to give FDA the additional tools to meet the new goals, the agreement provides for \$595 million in user fees over the life of the agreement. Additional reviewers, lower management-to-reviewer ratios, enhanced training and other resources totaling about 200 additional FTEs for the agency are provided by the agreement and will give FDA what it needs to improve performance.

Of course, no agreement, no matter how good on paper, is self-executing. Making it work as intended will require the full efforts of all concerned. Continued oversight and interest from the Congress will also be important. Patients are depending on all of us.

In conclusion, I should note that a number of legislation proposals have been introduced with the goal of improving FDA's operations also. We are appreciative of efforts by all members who seek to give FDA the tools and structure it needs to succeed. At the same time, I want to emphasize that we are strongly committed to the user fee agreement as negotiated and do not support any proposals that would change the terms of the agreement or undermine its goals. Just as the user fee agreement has the potential to help FDA move in a positive direction, failure to reauthorize the program in a timely way would be nothing short of catastrophic, as my colleagues on the panel have also echoed.

So I thank the committee for the opportunity to testify and urge it act promptly to reauthorize the program which is so critical to patients, to FDA and to our industry.

[The prepared statement of Mr. Levitt follows:]

**Testimony Summary of Joseph A. Levitt
Partner, Hogan Lovells US LLP
On behalf of the Advanced Medical Technology Association
House Energy & Commerce Health Subcommittee -- April 18, 2012**

- The U.S. medical technology industry is an American success story, directly employing more than 400,000 workers nationwide.
- Success in our industry comes only from innovation. We are very proud of our contributions to the U.S. economy and are even more proud of our contributions to improving patient care.
- FDA is a critical partner in our companies' efforts to bring safe and effective medical devices to patients. Without a strong, effective and efficient FDA, we cannot have a strong and competitive industry.
- While the FDA has consistently maintained a strong record of assuring safety and effectiveness of the products it reviews, delays in product approval, inconsistency in the review process, and the resulting downstream effects on investment and innovation have undermined the competitiveness of our industry and harmed patient access to new treatments, diagnostics, and cures.
- We are pleased that after extensive negotiations, FDA and industry reached a user fee agreement that has the potential to help achieve meaningful change in FDA performance through groundbreaking accountability and transparency measures and enhanced FDA resources.
- This user fee agreement establishes average total time goals for FDA product review. Total time is the best indicator of whether FDA is consistent and efficient in its review and is providing sponsors with adequate information in advance of what data is needed for different types of products. These total time goals are shared performance goals, because industry also has an obligation to submit good applications to FDA.
- The agreement also establishes improved goals for time on the FDA clock and the improved FDA goals and the total time goals work together to encourage FDA to focus on a thorough but efficient review of all product submissions.
- The agreement includes process standards that we anticipate will improve the consistency and timeliness of the review process, including meaningful presubmission interactions, midway review interactions, and a new process for submissions that are outside the FDA time target.
- The agreement provides greater accountability to industry, patients and to Congress and the Administration, through regular reporting on key metrics and an outside analysis of FDA's management of the review process, coupled with an FDA corrective action plan to address opportunities for improvement.
- Lastly, to give FDA additional tools to meet the new goals, the agreement provides \$595 million in user fees for 2013-2017.
- Each of the provisions of this agreement has the potential to make a difference in improving FDA performance, but the whole is truly greater than the sum of its parts.
- We urge the Committee to act promptly to reauthorize the MDUFA program and enact this agreement into law. Failure to act would not only jeopardize the critical improvements made by the new agreement but would have a devastating impact on our industry's ability to bring improved treatments and cures to patients.

**Testimony of Joseph A. Levitt
Partner, Hogan Lovells US LLP
On behalf of the Advanced Medical Technology Association
House Energy & Commerce Health Subcommittee
April 18, 2012**

Thank you Chairman Pitts, Ranking Member Pallone and members of the Committee for the opportunity to testify today.

My name is Joe Levitt, and I am a partner with the firm of Hogan Lovells US LLP. I am here today on behalf of the Advanced Medical Technology Association (AdvaMed), although my testimony today on the MDUFA agreement is submitted on behalf of three of the medical technology industry associations who participated in the MDUFA negotiations—AdvaMed, the Medical Device Manufacturers Association (MDMA), and the Medical Imaging Technology Association (MITA).

I want to thank you for convening today's hearing, and for your interest in improving medical device regulation for patients and industry. Over the course of the last year, members of this committee have demonstrated their focus on improving the efficiency and effectiveness of FDA regulation, and your outreach to the agency and the policy proposals that have been introduced show your commitment to this important issue.

The U.S. Medical Technology Industry

The medical technology industry is an American success story. Our industry directly employs more than 400,000 workers nationwide. Typically, for every worker our industry directly

employs, another four workers are employed by businesses supplying components and services to our industry so that the total number of employees generated by our industry exceeds two million.

The jobs our industry provides are good jobs—the kinds of jobs that allow employees to live the American dream. Industry pay levels are 38 percent higher than average pay for all U.S. employment and 22 percent higher than other manufacturing employment. While the number of manufacturing jobs was plummeting across the larger economy, even before the recent economic downturn, employment in our industry was expanding. Between 2005 and 2007, medical technology employment grew 20.4%, adding 73,000 jobs. During the recession, between 2007 and 2008, MedTech employment dropped 1.1 percent, compared to 4.4% for manufacturing as a whole.

Our industry is heavily skewed toward small companies—the kind of companies that begin with a doctor, an engineer, and an idea to improve patient care. Almost two-thirds of the 7,000 medical technology firms in the U.S. have fewer than 20 employees. A high proportion of the breakthrough products in our industry come from these small, often venture-capital funded companies.

And whether the firm is large or small, success in our industry comes only from innovation—the creation of diagnostics, treatments and cures that extend and enhance lives. Our industry's investment in research and development is more than twice the national average. Our product life-cycle is only 18-24 months.

Our industry is so competitive that price increases have averaged only one-quarter the rate of other medical goods and services and just one-half the general CPI for almost 20 years.

With \$33 billion in total exports in 2008, medical technology ranks eleventh among all manufacturing industries in gross exports. Notably, unlike virtually every other sector of U.S. manufacturing, medical technology has consistently enjoyed a favorable balance of trade. With the aging of both U.S. and foreign populations, the projected explosive growth of large middle class populations demanding modern health care in developing countries like China and India, and the accelerating pace of biomedical discovery, the potential for growth of our industry is great.

While we are very proud of our contributions to the U.S. economy, we are even more proud of our contributions to improving patient care. For patients, medical progress has been remarkable. Between 1980 and 2000, medical progress added more than three years to life expectancy. The death rate from heart disease was cut in half; the death rate from stroke was cut by one-third, and the death rate from breast cancer was cut 20%. Medical technology has been a major driver of this progress.

FDA Regulation of Medical Devices – MDUFA III

While we are making progress in improving patient care and see immense future opportunities to provide jobs and contribute to long-term economic growth, we are also worried. Today, America is the world leader in medical technology. But there are warning signs. As a recent

PriceWaterhouse Coopers report showed, our lead is slipping on a number of dimensions of competitiveness. And a key factor in our loss of competitiveness has been the decline in FDA's performance in ensuring timely patient access to safe and effective medical devices.

Put simply, FDA is a critical partner in our companies' efforts to bring safe and effective medical devices to patients. Without a strong, effective, and efficient FDA, we cannot have a strong and competitive industry. The predictability, consistency and efficiency of FDA decision-making, as well as reasonable, risk-based standards of evidence to assure the safety and effectiveness of medical technology products, is essential to drive new innovations for patients and for the long-term success of the medical device industry.

As a former FDA veteran of 25 years who served in a variety of capacities, including as Deputy Director for Regulations and Policy at the FDA's device center in the 1990's, I can tell you that FDA has consistently maintained a strong record of assuring the safety and effectiveness of the products it reviews. The hard working staff at FDA has always focused on patient safety as a top priority, and the data bear out their dedication to protecting the end users of medical devices.

At the same time, there has been slippage in FDA's track record of reviewing products in a timely and consistent manner. FDA has recognized this as well. Taken together, longer FDA review periods, inconsistency in the review process, and the resulting downstream effects on investment and innovation have lessened the competitiveness of our industry and harmed patient access to new treatments, diagnostics, and cures.

The user fee agreement reached between FDA and industry after extensive negotiations has the potential to help achieve meaningful improvement in FDA performance through groundbreaking accountability and transparency measures and enhanced FDA resources.

The FDA leadership and Dr. Shuren have recognized the need to vigorously address the issues affecting the device center and are already taking a number of steps that we believe have the potential to bring significant improvements. The user fee agreement has the potential to be an additional step in the right direction. It is good for industry. It is good for FDA. And most of all, it is good for patients.

We urge this Committee and the Congress as a whole to act promptly to reauthorize the user fee program and enact this agreement into law. Failure to act would not only jeopardize the critical improvements made by the new agreement but would have a devastating impact on our industry's ability to bring improved treatments and cures to patients.

The user fee agreement builds the conditions for success in a number major ways:

Total Time to Decision Goal

For the first time ever, this user fee agreement establishes the shared outcome goal of average total time to decision for FDA product review. All previous agreements have set goals in terms of time on the FDA clock. When the FDA asks sponsors for additional information or data, the FDA clock stops. The result was that, while FDA may have been technically meeting the goals

for 510(k) submissions in terms of FDA review times, the total average time from submission to final decision increased 43% when comparing the 2003 through 2007 timeframe with comparable data from 2010. Of course, what matters to companies and patients is not an artificial construct like time on the FDA clock, but rather the total time (including any necessary time spent by the device sponsor in answering FDA's questions) it actually takes to get a final decision from FDA.

We refer to this new performance metric as a shared performance goal. Under the agreement, industry has an obligation to submit good applications and to respond expeditiously to legitimate questions from FDA about an application, and FDA will have authority to decline to begin review of an application that is obviously deficient when it is submitted. We recognize that FDA cannot control the amount of time it takes for a sponsor to respond to questions about any individual application. What FDA can and should do better at, however, is communicating to device sponsors, in advance, what the data requirements are for a given device, so sponsors have maximum likelihood of getting it right the first time. This would, in turn, reduce the total time from submission to final decision. All sponsors want to submit applications that meet FDA standards, so transparency of data expectation is key to their success. We believe total time is the best indicator of whether FDA is consistent and efficient in its review and is providing sponsors with adequate information in advance of what data are needed for different types of products.

By setting in place this new goal, efforts will be focused on the metric that is truly most important to all concerned.

Improved FDA Day Goals

Second, the agreement also establishes significantly improved goals for time on the FDA clock. For example, in the case of PMAs receiving advisory panel reviews—which tend to be the most innovative products—90% of those PMA products will be receiving a decision within 320 days by the end of this agreement. The improved FDA day goals and the total time goals work together to encourage FDA to focus on a thorough but efficient review of all product submissions.

Process Improvements

Third, the agreement includes process improvements that we anticipate will improve the consistency and timeliness of the review process independent of the specific time goals.

The agreement provides for meaningful presubmission interactions between FDA and companies where agreements reached will not change, so that companies know what FDA expects and FDA is bound by its commitments, unless, of course, new information arises that requires a change to protect public health. As noted earlier, this is a key element for improving the efficiency of the device review program—communicating data requirements in advance so sponsors have maximum chance of getting it right the first time.

Additionally, there will be a substantive interaction between FDA and the company midway through the review process. This will assure that both companies and FDA identify any deficiencies in the application early, so that they can be corrected promptly.

Also, a new procedure that we call “no submission left behind” will be instituted, so that if the FDA time target is missed for 510(k) and PMA submissions, the company and the FDA will meet to work out a schedule for resolving remaining issues, so that the submission doesn’t go to fall off the radar screen.

Greater Accountability

Fourth, the agreement provides for greater accountability. Greater accountability means that FDA’s success under this agreement will be transparent to FDA management, to industry, to patients, and to Congress and the Administration, so that any problems that arise can be corrected promptly. Under the agreement, there will be quarterly and annual reporting on key metrics, providing reliable and consistent tracking of new performance indicators that both FDA and industry have agreed are important.

In addition, the agreement requires an analysis of FDA’s management of the review process by an independent consulting organization, coupled with an FDA corrective action plan to address any identified inefficiencies and provide opportunities for improvement. We were gratified during the negotiations with FDA that the agency welcomed this independent review as a way to

bring fresh eyes to the issues and work constructively towards meaningful process improvements.

Appropriate Resources

Finally, to give FDA additional tools to meet the new goals, the agreement provides \$595 million in user fees for 2013-2017. Additional reviewers, lower manager-to-reviewer ratios, enhanced training, and other resources provided by the agreement will give FDA what it needs to improve performance. Overall, the agreement will allow FDA to hire approximately 200 additional FTEs, the vast majority of which will be put into place where needed most – additional reviewers. This, coupled with additional supervisors who are being hired this year, should lead to improved consistency in the review process.

Each of the provisions of this agreement has the potential to make a difference in improving FDA performance. But the whole is truly greater than the sum of its parts. Each of the elements of the agreement reinforces the others. For example, as I noted earlier, the combination of total time goals and faster FDA time goals should result in greater improvements than either one would achieve separately.

And, of course, no agreement, no matter how good on paper, is self-executing. Making it work as intended will require the full efforts of FDA's dedicated staff and managers. Our industry is

committed to work with FDA in any way we can to make it a success. Continued oversight and interest from the Congress will also be important. Patients are depending on all of us.

Legislative Package

In addition to the underlying user fee agreement, a number of legislative proposals have been introduced with the goal of improving the FDA's operations. We are appreciative of efforts by all Members who seek to give the FDA the tools and structure it needs to succeed, and are encouraged by the package of legislative reforms released by the committee. Legislative reforms that do not alter the substance of the negotiated agreement between FDA and industry and seek to improve consistency and predictability in the FDA device review process hold the potential to create a legislative reauthorization package that maximizes the opportunity for success at the agency, which should be the shared goal of all involved.

For example, legislation has been proposed to streamline the de novo process by eliminating the statutory requirement that a sponsor receive a finding of "not substantially equivalent" before even beginning the de novo process. FDA itself has recognized that the current process is cumbersome, and FDA is looking at using its regulatory discretion to improve that process. However, statutory change may be the most effective way to address the problem, which will help FDA, industry, and ultimately patients.

There is also a proposal to address the confusion created by FDA's draft guidance regarding when, under the FDCA, a modification to a cleared device requires the submission of a new

510(k) application. Left in its current form, this draft guidance could be interpreted as establishing a standard that requires a new 510(k) submission for almost every modification. This has the potential to dramatically increase the number of 510(k) applications required, with no related public health benefit. According to a survey of AdvaMed members, this has the potential to increase submissions by 300 to 500%. This could serve to seriously impact patient access to medical devices, increase FDA's workload and put pressure on agency resources. We believe Congress should provide clarity and certainty that the existing approach to device modifications is appropriate.

In addition, the committee's legislative package seeks to address FDA's new approach to the investigational device exemption, or IDE. In the preamble to the IDE final rule, an IDE is described as "conditions under which investigations of medical devices involving human subjects may be exempt from certain requirements of the Federal Food, Drug, and Cosmetic Act . . . to permit devices to be shipped for clinical investigations to determine their safety and effectiveness." We believe the IDE review and approval process therefore should focus on the determination of whether the anticipated benefits of the device outweigh risks to human subjects, the importance of the knowledge to be gained and whether the investigation is scientifically sound. This new FDA policy is not only inconsistent with the regulation but is counterproductive from a public health point of view. It has been a major factor in slowing down the clinical trial process and extending the time it takes a product to get to market. It requires FDA to make early stage judgments that should appropriately be reserved for product clearance or approval. It has encouraged reviewers to try to resolve every possible trial design question in advance, making the trials themselves more cumbersome and costly than may be

necessary. FDA's apparent expansion of authority to include the additional determination of whether an investigation is sufficient to support product approval or clearance is not appropriate, and goes beyond what is contained in the statute and in the regulation. IDE approval should not be tied to product approval, but rather, should be based on what the clinical study is intended to do.

These are but a few examples of areas that we believe are appropriate to consider as legislative reforms to accompany the user fee agreement. At the same time, I want to emphasize that we are strongly committed to the user fee agreement as negotiated and do not support any proposals that would change the terms of the agreement or undermine its goals. Further, any legislative reforms should strike the appropriate balance between giving FDA the appropriate tools while preserving companies' due process rights so that innovative, life-improving and life-saving products can receive proper consideration.

I thank the Committee for the opportunity to testify and urge you to act promptly to reauthorize the user fee program, which is so critical to patients, to the FDA and to our industry.

Mr. PITTS. The chair thanks the gentleman.

We are in the middle of a vote on the floor. We have about 10 minutes. We will take one more witness and then we will break for the vote.

Mr. Coukell, you are recognized for 5 minutes.

STATEMENT OF ALLAN COUKELL

Mr. COUKELL. Thank you, Mr. Chairman, Ranking Member Pallone and committee members. I appreciate the opportunity to testify.

My name is Allan Coukell, and I am the Director of Medical Programs for the Pew Health Group. Our research and analysis aim to improve the safety and well-being of American consumers with the major focus on drugs, medical devices and the FDA. I will focus today on the importance of the FDA user fee agreements to patients and public health and about three key policy areas that the committee is considering.

Since 1992, PDUFA agreements have given FDA significant and sustained resources, allowing for faster reviews of new products. Indeed, preliminary results of a study that Pew has funded show that FDA reviews drugs faster than its counterparts in the E.U. and Canada. The development of new antibiotics is a particular focus for Pew's Antibiotics and Innovation Project, and we thank this committee for consideration of the GAIN Act, the bipartisan bill introduced by Mr. Gingrey that would grant extra market protection to certain antibiotics.

Unlike other drugs, antibacterials lose their effectiveness over time as the bugs become resistant. That is why experts are so alarmed about the years-long decline in new antibiotics and the dearth of products in late-stage development. We look forward to working with this committee to see that this provision targets and incentivizes the drugs we most need, those that treat serious or life-threatening infections.

Turning now to medical devices, we ask Congress to swiftly reauthorize MDUFA. Under this new agreement, FDA would add 200 device staff and nearly \$600 million for the review of device applications. Let me illustrate the importance of this funding with an analysis recently commissioned by Pew showing that FDA's Device Center has a higher attrition rate than the Centers for Drugs and Biologics or the Office of Regulatory Affairs. In fact, nearly 10 percent of FDA's device staff left in fiscal year 2010, and the majority reported not having sufficient resources to get their job done. To function effectively, the center must have adequate funding.

But let us never forget that true innovation is not just about speed to market but about developing products that are safer or more effective than existing drugs and devices, and because medical devices often enter the market with little or no clinical data, it is especially important that we have a robust system for postmarket surveillance, and we urge this committee to include legislation that will medical devices to FDA's Sentinel Surveillance System which is currently on for drugs, require that FDA issue and implement rules that assign a unique identifier like a barcode to each new device as we have on most other things that we buy, and clarify the agency's authority to order safety studies when nec-

essary for high-risk devices. We must also ensure that these studies are completed in a timely way. Such a system would detect safety problems faster and would facilitate innovation by increasing the confidence of the public and the FDA on marketed devices.

On safety, I am pleased to note that the landmark new generic drug user fee agreement while speeding the review of these products will also enhance safety by ensuring that FDA performs more inspections of overseas generic drug plants. As Pew's drug safety project has noted, 80 percent of the ingredients in our drug supply now come from overseas yet we inspect U.S.-based drug makers every 2 years, as the law requires. Meanwhile, the FDA inspections in China, for example, average out about every 17 years. Addressing this disparity will level the playing field for U.S.-based manufacturers and help to protect patients. Congress should hold FDA accountable by ensuring that no facility goes indefinitely without an inspection. But inspections are only part of the story. Several additional key measures would improve confidence in the supply chain.

For example, we should ensure that every company takes responsibility for its own upstream suppliers, verifying that appropriate quality systems are in place. We should reward manufacturers who have strong systems. We support a national track-and-trace system for drugs but such a system must include standards that will detect counterfeits before they get to patients and, for example, provide law enforcement with the tools needed to address illegal-drug diversion.

We thank the committee for its bipartisan work on the prescription drug supply chain. A poll we commissioned showed that Americans of all political persuasions recognize the risks and support Congressional action.

I will conclude with a reference to FDA's mission statement, which acknowledges the agency's dual role: protecting patients and ensuring innovation. The user fee agreements support both aims, and we urge Congress to pass them quickly along with the three essential additions: drug supply chain safety, antibiotic development and medical device safety.

Thank you, and I welcome your questions.

[The prepared statement of Mr. Coukell follows:]

**Summary Testimony before the
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
April 18, 2012**

Allan Coukell, Director of Medical Programs, Pew Health Group

Since 1992, user fee agreements have given FDA significant and sustained resources that allow the agency to review new products quickly. In fact, preliminary findings of a study that Pew has funded show that FDA reviews new drugs faster than its counterparts in the European Union and Canada.

The user fee legislation is also an important opportunity to consider key updates to the Food, Drug and Cosmetic Act that will protect Americans and support innovation, in particular:

- **Drug supply chain safety:** FDA needs regulatory systems that are appropriate for today's global supply chain.
- **Medical device safety and innovation:** We urge the Committee to include legislation to create a more robust system of post-marketing surveillance, which would promote safety by identifying problematic medical devices more quickly. It would also facilitate innovation by increasing confidence in the safety of medical devices on the marketplace.
- **Antibiotic development:** We urge the Committee to include the Generating Antibiotic Incentive Now Act, which would provide economic incentives to stimulate the development of new antibiotics.

The user fee agreements are essential to an effective FDA that can foster innovation while ensuring the safety and efficacy of the products we depend. We urge Congress to swiftly reauthorize this program with three important additions - drug supply chain safety, medical device safety and innovation, and antibiotic development.

**Testimony before the
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
April 18, 2012**

Allan Coukell, Director of Medical Programs, Pew Health Group

Chairman Pitts, Ranking Member Pallone, and members of this committee, thank you for the opportunity to testify about the importance of the user fee agreement (UFA) legislation to patients and public health. I am also pleased to discuss three key policy initiatives that should be considered along with the UFA legislation.

Based on data, science, and non-partisan research, 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. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and stimulate civic life.

Since 1992, user fee agreements have given FDA significant and sustained resources that allow the agency to review new products quickly. In fact, preliminary findings of a study that Pew has funded show that FDA reviews new drugs faster than its counterparts in the European Union and Canada.

Medical device user fees are especially important for the review of devices. An analysis commissioned by the Pew Health Group compared the Center for Devices and Radiologic Health (CDRH) with the Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, and the Office of Regulatory Affairs. The report reveals that CDRH has the highest annual attrition rate of the four centers, with nearly 10 percent of the center's science, technology, and engineering staff leaving in FY 2010. Resource issues may help explain the high attrition rates; less than half of CDRH employees surveyed agreed that their workload is reasonable and even fewer reported having sufficient resources to get their job done. For it to function as efficiently and effectively as possible, CDRH must have adequate funding.

The user fee agreement would provide FDA with additional resources to review applications and add about 200 much-needed staff members to the agency. The total fees collected over the five year period from 2013 to 2017 are expected to reach \$595 million, a significant increase over the previous agreement. This will help create a more efficient center that is sufficiently resourced to better protect consumer safety and facilitate the introduction of innovative devices.

The landmark new Generic Drug User Fee agreement will hasten the review of generic drugs, as well as ensure that FDA has the resources – and the mandate – to conduct more frequent inspections of overseas drug manufacturing facilities. We urge you to pass these bills swiftly to ensure that FDA can continue its important public health activities uninterrupted.

The user fee legislation is also an important opportunity to consider key updates to the Food, Drug and Cosmetic Act that will protect Americans and support innovation. I would like to discuss three particular issues that Congress is considering and urge you to include them as part of the user fee reauthorizations:

- Drug supply chain safety,
- Medical device safety and innovation, and
- Antibiotic development.

Drug supply chain safety

Many Americans would be surprised by the rapid and profound changes in how our prescription drugs are made – and the new risks this process brings. Today, 40 percent of all finished pharmaceuticals, and 80 percent of the active ingredients and bulk chemicals in U.S. drugs, are sourced from foreign countries.

Yet FDA oversight of manufacturing has not kept pace with these changes. This puts consumers at risk and American manufacturers on an uneven playing field. While the best companies are already doing thorough assessments of their supply chains, we must make sure there is no incentive for the weaker actors to gain a competitive advantage by cutting corners.

FDA needs regulatory systems that are appropriate for today's global supply chain. I've already mentioned that the GDUFA agreement will increase FDA's ability to conduct foreign inspections. However, there is more that must be done. We should ensure that every company has appropriate supply chain controls in place, and that companies that do have such systems will not face delays at the border. At the same time, FDA needs the clear authority to refuse products when the plant that made them has denied an FDA inspection.

Today, a plant outside the U.S. knows FDA may visit only once, before the product is first approved, and then never return. That reduces the incentive to make ongoing investments in quality. The FDA should inspect plants, both domestic and overseas, based on risk, which will permit the Agency to make much more efficient use of its limited resources. However, no plant should go indefinitely without an inspection. A minimum frequency of 4 years should also be established.

Risks to the drug distribution system

The United States currently has no national system to detect or prevent incidents of counterfeiting and drug diversion. Although incidents in the U.S. are far less common than in other parts of the world, a recent example illustrates the serious nature of the risks. In February, FDA warned that cancer patients in the U.S. were exposed to counterfeit Avastin® – a critical chemotherapy agent used to treat numerous cancers. Just two weeks ago, the FDA warned that it had discovered yet another batch of counterfeits of the same drug, this time being sold in the United States under the drug's Turkish brand name.

Congress is considering an industry proposal that would result in a unique serial number being affixed to each package of drugs. While this proposal contains some good elements, including national standards for wholesaler licensure, it falls short in two crucial respects. First, the industry proposal calls for keeping track of drugs only by lot number, and a lot may include thousands of vials distributed across numerous wholesalers and pharmacies. Second, the proposed system would not routinely check for, or identify, counterfeit drugs.

However, there is a way forward. We urge the Committee to ensure that any national track and trace legislation include a date certain for unit-level traceability and for routine checks – known as authentication – to detect counterfeits.

Medical Device Safety and Innovation

Medical devices are important in improving the health of many Americans. These products include, for example, artificial hips, pacemakers, and ventilators. However, as with all medical products, there are risks associated with devices, which often enter the market with little or even no clinical data.

We urge the Committee to include legislation to create a more robust system of post-marketing surveillance, which would promote safety by identifying problematic medical devices more quickly. It would also facilitate innovation by increasing confidence in the safety of medical devices on the marketplace. This system would require:

- Adding medical devices to the Sentinel, FDA’s active surveillance system – currently solely for drugs;
- Requiring that FDA issue and implement rules that assign new devices a unique identifier, like a barcode;
- Clarifying FDA’s authority to order safety studies, when necessary, for high-risk products that will be used in patients – and ensuring that these studies are completed in a timely fashion;
- Clarifying that FDA can order short-term studies, known as 522 studies that assess safety and efficacy at the time a device is approved or cleared. Manufacturers would have a year to commence this post-marketing study.

We also urge Congress to give FDA the authority to classify medical devices as high, medium, or low risk without going through a lengthy regulatory process. In fact, *new* device types already can be classified by FDA in this manner. This will help ensure that devices enter the marketplace with the appropriate amount of testing—neither too much nor too little.

I would also like to comment on some of the proposals the Committee is actively considering:

1. Streamlining the *de novo* pathway: We are pleased that the Committee is considering striking the requirement that certain novel devices first go through the 510(k) process. This can speed the approval of these products without jeopardizing safety. Under current law, FDA has 90 days to review a 510(k) notification for a device that is substantially equivalent to a device that FDA has reviewed before. For a streamlined *de novo* pathway for truly innovative devices to work, FDA needs at least 120 days to properly review the new devices.
2. Changing the Investigational Device Exemption: The Committee is considering a proposal which would lower the standard by which FDA approves a clinical trial. Since even seemingly low-risk clinical trials have the potential to cause harm to the patients who agree to participate in the trials, Congress must ensure that clinical trials for untested medical devices will only be conducted if they are designed to meet the ultimate endpoints for devices: safety and efficacy.
3. Changes to rules about modifying 510(k) devices: This legislation could jeopardize patient safety by undermining FDA's ability to determine which changes to a device require a full or partial 510(k) application. The agency already has clear guidance for manufacturers about the level of documentation required for different types of changes to product design. Under the current system, minor changes require only a note to the file.
4. Voidance of guidance documents: The Committee is considering legislation that would automatically void draft guidance documents if they are not finalized within 12 months. While we share the view that FDA should finalize guidances as quickly as possible, we are concerned that this policy could have unintended consequences. First, it could divert finite FDA resources away from issuing new guidance, and, secondly and more importantly, an automatic voiding of draft guidance would leave manufacturers with even less clarity about regulatory expectations. Instead of automatic expiration of draft guidance, we propose that Congress require FDA to give regular reports on the reasons

guidances are delayed and also to provide a timetable for the finalizing of guidances that have been in draft for longer than 18 months.

5. Changing FDA's mission statement: FDA's mission is to assess the safety and effectiveness of the products it regulates while, at the same time, making sure that innovative products get to market in a timely way. Changes to the FDA mission statement should not dilute these important goals. For example, we are concerned that there could be significant unintended consequences from adding job creation and economic growth to FDA's mission statement. No product developer should have to wait on an approval decision while the FDA conducts an economic analysis. Moreover, beneficial technologies are sometimes disruptive. No life-saving device should be delayed because it will take the place of some other less effective product made by a company that may employ more people.

Generating Antibiotic Incentives Now (GAIN) Act

Let me turn to a third area, one where innovation is essential – the development of new antibiotics. Antibacterial drugs are unlike other medicines. Most drugs retain their effectiveness forever. But bacteria inevitably become resistant. Alas, the number of new antibiotics has been dwindling. Today, we find ourselves on the brink of what the Centers for Disease Control and Prevention Director Dr. Thomas Frieden has warned could be a “post-antibiotic era.”¹

We wish to thank Rep. Gingrey, Rep. Green, and their fellow co-sponsors of H.R. 2182, the Generating Antibiotic Incentives Now (GAIN) Act, for their bipartisan leadership on this important legislation that will stimulate the development of new antibiotics. This bill enjoys broad support in both chambers of Congress and on both sides of the aisle.

The GAIN Act builds on precedents set by laws such as the Orphan Drug Act. It would grant an economic incentive for the development of new antibiotics by granting additional exclusivity – that is freedom from generic competition – for certain qualified products. We recognize that this is not a change that Congress undertakes lightly, and Pew is working with Members of Congress to ensure that the bill squarely targets the development of the most-needed new drugs—those to

treat serious or life-threatening diseases, such as healthcare-associated and community-acquired pneumonia, complicated skin, intra-abdominal and urinary tract infections, sepsis, tuberculosis, meningitis, and other infections of vital organs and systems.

Conclusion

The user fee agreements are essential to an effective FDA that can foster innovation while ensuring the safety and efficacy of the products we depend. We urge Congress to swiftly reauthorize this program with three important additions - drug supply chain safety, medical device safety and innovation, and antibiotic development.

Thank you, and I look forward to answering any questions.

¹ *Antibiotic Resistance and the Threat to Public Health, before the Committee on Energy and Commerce, Subcommittee on Health, United States House of Representatives, 111th Congress, 2nd Session (2010)* (statement of Thomas Frieden, M.D., M.P.H., Director, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services).

Mr. PITTS. The chair thanks the gentleman.

That concludes the opening statements. We are in the middle of a vote. I think we have about 5 minutes left, so at this point the subcommittee will break until the third vote. Five minutes after the third vote, we will reconvene. The subcommittee stands in recess.

[Recess.]

Mr. PITTS. The recess having expired, we will reconvene the Subcommittee and go to the questioning. I will now begin the questioning and recognize myself for 5 minutes for that purpose.

First of all, Dr. Wheadon, how does the PDUFA agreement help mitigate the issue of delayed reviews of drug applications at FDA and help America maintain their role as the leading innovator in the pharmaceutical space? If you would please elaborate on that.

Dr. WHEADON. I will answer that, Chairman Pitts, on two fronts, focusing initially on the New Molecular Entity—

Mr. PITTS. Is your microphone on? Just pull it down. Yes.

Dr. WHEADON. Focusing initially on the New Molecular Entity Review Program, that was really set up to enhance ongoing communication between drug sponsors and FDA such that sponsors would understand up front what FDA expectations may be as they enter into the review. As the review progresses, there would be feedback to the sponsor. There are questions that come out of the review that could be answered contemporaneously rather than waiting until the end of the review. The intention is that by the time you get to the end of the review, most of the issues could have been discussed and hopefully rectified, allowing for FDA to make a final action, hopefully an approval, thus allowing the drug to be approved in the first cycle and available to patients.

Beyond that, the other aspects of the agreement, the availability of innovative medicines to patients, really looks at the regulatory science initiatives, things like benefit-risk, biomarker development, pharmacogenomic processes, enhancing the utilization of REMS in terms of standardizing that process rather than starting from square one with each necessity for utilizing of REMS for approval.

So taken as a whole, the intention is to make the review process more efficient and more effective use of FDA resources, allowing for a thorough review but hopefully a one-cycle review and ultimately really addressing the issue that we started out looking at, and that is for roughly 50 percent of applications, they don't get approved in the first cycle. They ultimately do get approved with following cycles of review. That is an inefficient use of FDA resources and that is really what we are trying to tackle with the agreement.

Mr. PITTS. Ms. Radcliffe, would you like to add to that as far as bio is concerned?

Ms. RADCLIFFE. Yes, I would. Thank you. I would like to support everything that Dr. Wheadon said about the weight of the PDUFA Technical Agreement will enhance the availability of products for patients but mention also one other thing. It was particularly important for our small companies and that was a provision to enhance timely interactive communication during the drug development phase. Our small companies tell us that very often they have simple, informal questions where they need timely answers in order to proceed. We were very pleased that the Agency agreed to

state explicitly that they have a philosophy of timely, interactive communication with sponsors and also that we were able to agree to establish a liaison staff that would work to ensure that that communication occurs.

Mr. PITTS. Thank you.

Mr. Gaugh, the discussion draft includes a section on expediting manufacturing changes to alleviate a drug shortage. Would you comment on this provision, tell us how it would help?

Mr. GAUGH. I am sorry. Could you repeat that?

Mr. PITTS. Yes. The draft includes a section on expediting manufacturing changes to alleviate drug shortages. Comment on that provision.

Mr. GAUGH. Yes, in today's environment it takes anywhere from 18 to 24 months for those review cycles to occur, so if you have a product that is in drug shortage, that is an additional time point with everything else that you are adding to it. The provisions in here are going to be for expedited review, which could be as quickly they say as 3 to 6 months, which would help tremendously.

Mr. PITTS. Mr. Levitt, can you explain IDEs—what are they, what companies get IDEs traditionally, how does FDA evaluate IDEs? I understand FDA has a new policy on IDEs. How does that differ from previous policy and what is your opinion of the new policy?

Mr. LEVITT. OK. An IDE stands for Investigational Device Exemption. What it basically means is that FDA reviews applications for new clinical studies. New clinical studies are needed generally for all Class 3 devices going through the premarket approval process and for a small minority of 510(k) products. But if a company wants to test their device in humans and it doesn't fit into one of the minor categories that they are exempt from submitting, then they submit an application to the FDA that includes the data to show that the device is safe enough to test in humans. So the first question is safety. And the second question is, what is the protocol that they are going to use during the study? They will submit those to FDA. FDA has 30 days only to review that, reflecting that FDA's review is really just to focus on is it safe and is this essentially a bona fide study where the potential benefits outweigh the potential risks. So that is the historical process.

What has happened recently is that FDA has brought greater scrutiny to the clinical protocol part and they are trying to say that you can only do this clinical study if it is good enough to get final approval. And there is a lot of concern within the industry that that is much more than has ever been done in the past and is certainly much more than the regulations their statute require, that the process should be able to go forward at the pace that the company is prepared to undertake. It might be a preliminary study, it might be a study that will depend on how strong the results are, how big you need.

And so I think the concern that you are hearing is that that study should not be the most robust possible, but instead, the FDA should allow the study to go forward if it is safe and if it is bona fide research where the potential benefits outweigh the potential risks and there is valid information to be learned from the study.

That essentially is the company's call on how they want to investigate the device and develop the program.

Mr. PITTS. The chair thanks the gentleman. My time is expired. The ranking member is recognized for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to start with Mr. Gaugh. I appreciated GPhA's support for the bill that Representative Guthrie and I recently introduced, the Generic Drug Application Review Fairness Act. We heard earlier from Dr. Woodcock about the long review times for generic drug applications that currently exist. If the median review time for generic drug applications currently exceeds 30 months, how does that impact the generic manufacturers and what are the consequences if you will?

Mr. GAUGH. Well, you heard in earlier testimonies if you go back to the statute that it is 6-month review time, which we are well, well past that, 30 months, so almost 2 years past the statute. So in that 2-year time point, once you have put your drug application in, market dynamics can change significantly in that additional 2 years. So it may be a situation where by the time the 30 months has expired, the market is not still effective for the company to get into. That is one issue.

Mr. PALLONE. And what about the significance of the 180-day exclusivity period for generic firms?

Mr. GAUGH. The 180-day exclusivity has become a real factor because in that approval process, it affects first-filers in paragraph 4 certifications, and if you don't have the product approved or tentatively approved by the FDA within that 30-day time point, you lose your 180-day exclusivity.

Mr. PALLONE. Do you know how many applications since maybe 2003 have unfairly lost the 180-day exclusivity because of the FDA review delay?

Mr. GAUGH. Somewhere in the range of 8 to 10.

Mr. PALLONE. OK. I mean, it seems to me that the increasing meeting of approval time of generic drug applications is unintentionally placed into jeopardy the 180 days of exclusivity rewarded to the generic applicants, and I am hopeful that my colleagues will support inclusion of the Generic Drug Application Fairness Act into the User Fee package, which is being considered, because this would at least temporarily fix the consequences that you discussed.

Let me ask Mr. Wheadon, if you would, we heard from Dr. Woodcock a little bit ago that there is added language to the discussion draft that was not part of the negotiated PDUFA agreement, and in FDA's view, these extensive reporting requirements would place a burden on the Agency and could result in an unwarranted reshuffling of resources in other areas. What is PhRMA's view on this added provision?

Dr. WHEADON. Well, there are two aspects to consider. In many meetings with the FDA we have asked for data going down to the division level so that we can see whether or not there were some learnings to be garnered in terms of divisions that actually are more efficient versus those that may not be as efficient. Having said that, we also recognize that we don't want to burden the Agency with a panoply of measurements coming out of the PDUFA agreement. As Dr. Woodcock described, that may have the unin-

tended effect of diverting resources from the needed activities of reviewing applications and getting those applications acted upon. So it is a very nuanced position if you will that in terms of getting data down to the review division can be useful and we certainly have asked for such data, but we don't want to have so many measurements loaded onto the Agency such that they aren't able to do the basic work that they are there to do.

Mr. PALLONE. But I mean you said—and I think she said—that this wasn't part of your original agreement, correct?

Dr. WHEADON. The review division data was not part of the original, no.

Mr. PALLONE. OK. You are kind of answering it but, you know, I know you are trying to kind of—you are expressing your concern that we have to be careful but I guess my concern would be even if we knew that FDA could fail to accomplish other activities because of the need to shift their times and resources, you know, do you think that adding that would make sense if that were the consequence?

Dr. WHEADON. Certainly if it was resource-neutral, if we could, for example, substitute review division data for other measurements that are currently being collected such that the resources are not diverted from needed activities along drug approval—

Mr. PALLONE. Yes, but she said that is not likely.

Dr. WHEADON. But if there are ways that you can do it and not be overly burdensome, we would be supportive of getting review division data.

Mr. PALLONE. I think that we all agree that we have to be careful. If we were to tinker with the negotiated language that PhRMA signed off on we could very well hinder FDA's ability to accomplish their other performance goals. So I think you are basically expressing the view that you wish there were some way to accomplish this without jeopardizing the other.

Dr. WHEADON. Exactly.

Mr. PALLONE. All right. Thanks. My time is completed. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman. I recognize the vice chairman of the subcommittee for 5 minutes for questions.

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

Mr. Levitt, let me ask you a question just so I have my facts correct. Your previous experience was as a deputy director at the Center for Devices and Radiological Health?

Mr. LEVITT. That is correct. I was deputy director for regulations and policy.

Mr. BURGESS. And currently, you are with the Medical Device Manufacturers, is that correct?

Mr. LEVITT. Currently, I am a lawyer at the law firm Hogan Lovells, and I am representing AdvaMed and the other trade associations here today.

Mr. BURGESS. In either role, can you imagine a scenario where it would be a company's business plan to go to market with something that they knew was flawed and going to cause harm or damage to patients? Would that be a viable business strategy?

Mr. LEVITT. It is hard for me to imagine anybody having that business strategy.

Mr. BURGESS. But you have heard the exchanges this morning between Mr. Markey and Dr. Shuren, myself and Dr. Shuren. Do you have any thoughts on what you have heard this morning? Do you think there is a risk out there that rogue companies are going to be putting damaging products out there on the market that the FDA's hands are essentially tied and they can't do anything?

Mr. LEVITT. I think it is hard for me to believe that there is a significant issue, problem there that needs legislation. The reviewers have enormous latitude to ask questions on devices. There almost always are incremental differences between new devices and old ones, and as has been pointed out, even after a final 510(k) decision is made, the Agency has additional authorities to prevent adulterated or misbranded devices from going onto the market. It is hard for me to believe—and Dr. Shuren, I thought, said as much—that the Agency doesn't believe it has let out onto the market unsafe devices.

Mr. BURGESS. And just from where I sit here, that was pretty troubling. Even if there is only a handful, we really need to know those devices and where the system failed us if that is happening. And I am with you. I cannot believe that it actually is happening. In today's medical legal climate, I don't think a company could exist if it pursued such a strategy.

Mr. LEVITT. Right. I think we would have to see the examples, but I can't imagine any company going in with a business plan to say I am going to sell a flawed device.

Mr. BURGESS. Additionally—and of course your testimony and, Mr. Coukell, I think your testimony as well—the indication was that specifically the Center for Devices and Radiological Health required an additional 200 employees. Did I pick up that information correctly?

Mr. COUKELL. Yes, sir, that is a consequence of the User Fee Agreement that has been negotiated between the industry and FDA.

Mr. BURGESS. And will these 200 new employees, will they be housed at White Oak or will they be reviewers out somewhere else in the country or will they be put on the job inspecting manufacturing plants? Where do they go? I visited Dr. Shuren. It is very lovely and spacious offices out there at White Oak, but I didn't see space for 200 more people.

Mr. COUKELL. Well, there is a lot of construction out there, sir, but I don't know the answer to that.

Mr. BURGESS. OK. So we are expanding government in the process of doing this. And I am not disputing that they are not necessary, but at the same time, maybe, Mr. Chairman, we can, as a written question, follow up to Dr. Shuren. We can get a breakdown on the activities and duties of those 200 new personnel that are going to be hired under the monies provided by the User Fee Agreement.

Ms. Radcliffe, let me ask you a question. I have worked on the issue of conflicts. 2007, when the reauthorization was done that year, I thought the language on conflicts went a little bit too far and was too restrictive. Do you think that the concerns I had that day in June were justified about the conflicts language being a little too restrictive?

Ms. RADCLIFFE. We do and we thank you very much for your work on that issue. The conflicts of interest are extremely important and we respect the need to ensure that conflicts of interest don't affect the way—

Mr. BURGESS. Correct.

Ms. RADCLIFFE [continuing]. That FDA does its very important work. That being said, we have heard from many stakeholders that the provisions that were put in place have limited FDA's ability to put the right expertise on its advisory committees, and that is also I think of great concern to patients and certainly to industry. And so we appreciate the effort to return FDA to being governed by the same conflict-of-interest provisions that the rest of the U.S. Government is governed by.

Mr. BURGESS. And certainly I want to thank you for working with committee staff to try to get that issue resolved.

Mr. GAUGH, let me just ask you a question. I mean drug shortages come up every time we have a hearing such as this. Do you have an opinion as to is there enough in the User Fee Agreements, the draft that you have, is there enough in there to deal with the issue of drug shortages from the generic manufacturers' standpoint?

Mr. GAUGH. We believe that the draft, including to the draft would be the private stakeholder group, the ARI, Accelerated Recovery Initiative. Between those two, there would be enough, yes.

Mr. BURGESS. Let me ask you this. Sometimes it occurs to me that maybe we have tightened things down too much, that the hyper-competition that has been introduced into the marketplace has made it unprofitable for a manufacturer to continue manufacture of something. And then if a problem occurs with their manufacturing floor, they just say forget it. I am out of the business. Is that in fact happening?

Mr. GAUGH. I think part of the answer to that is, as Dr. Woodcock said today, the majority of the drug shortages in our environment as we see today is the sterile injectables, and sterile injectables are a highly sophisticated process and there is really only a handful in the United States that make the sterile injectables. So when an issue happens with the line, as you have said, that puts a severe crunch on the entire pipeline.

Mr. BURGESS. OK. Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member emeritus, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Thank you, Mr. Chairman.

And again, I want to thank you for this hearing but I also want to thank my colleague, Mr. Murphy, for working with me on the important system and issue of priority in inspections. These questions will go first to Mr. Gaugh.

Mr. Gaugh, yes or no, under the User Fee Agreement negotiated by the generic drug industry, your industry is committed to paying additional fees to ensure that both foreign and domestic manufacturers are held to the same inspection standards? Is that correct? Yes or no?

Mr. GAUGH. Yes.

Mr. DINGELL. And I believe that it is in good part because you are concerned that our domestic industry is inspected rather more

and is policed rather more carefully than the foreigners, is that right?

Mr. GAUGH. Yes.

Mr. DINGELL. Now, again, Mr. Gaugh, yes or no, these additional fees will ensure foreign and domestic manufacturers are held to the same inspection frequency and standards? Is that correct?

Mr. GAUGH. Yes.

Mr. DINGELL. Now, again, if you please, the same inspection frequency as agreed to by FDA and the generic drug industry under the User Fee Agreement is routine inspection every 2 years, is that correct?

Mr. GAUGH. That is correct, yes.

Mr. DINGELL. Now, again, do you agree routine inspections with parity between foreign and domestic manufacturers will help level the playing field for your industry? Yes or no?

Mr. GAUGH. Yes.

Mr. DINGELL. Is it fair to say that those in your industry are comfortable with being inspected every 2 years?

Mr. GAUGH. Yes.

Mr. DINGELL. Now, thank you for your kindness.

Mr. Coukell, these questions for you, yes or no again to the degree you can. FDA is currently required by the Federal Food and Drug and Cosmetic Act to conduct a GMP inspection of domestic drug manufacturers every 2 years. Is that correct?

Mr. COUKELL. Yes, sir.

Mr. DINGELL. Many have proposed removing the requirement for biannual inspections and instead moving to a fully risk-based inspection system with no minimum inspection frequency. FDA currently uses a fully risk-based approach for inspections of foreign drug manufacturing facilities with no minimum inspection frequency. Is that correct?

Mr. COUKELL. Yes.

Mr. DINGELL. Under this approach, how is FDA currently inspecting foreign drug manufacturing facilities?

Mr. COUKELL. We look at all facilities outside the U.S. it is about every 9 years. If we look at China, for example, it is about every 17. Those are averages that come from the GAO.

Mr. DINGELL. Now, would a fully risk-based inspection schedule guarantee that no drug manufacturing facility went indefinitely without an inspection?

Mr. COUKELL. No.

Mr. DINGELL. But it could, could it not?

Mr. COUKELL. Would a fully risk-based system—

Mr. DINGELL. Yes.

Mr. COUKELL [continuing]. Guarantee that—

Mr. DINGELL. Yes, if it just says that we are going to do this on the basis of risk, they could say, well, we don't find any basis for inspecting this particular facility.

Mr. COUKELL. Yes, I agree with you.

Mr. DINGELL. OK. Now, would a minimum inspection frequency provide regulatory certainty to our drug manufacturers, promote parity between our domestic and foreign drug manufacturers, and better protect the public's health and safety?

Mr. COUKELL. Yes, it would.

Mr. DINGELL. Mr. Chairman, I am giving you back a minute and 14 seconds.

Mr. PITTS. The chair thanks the gentleman.

Mr. DINGELL. Thank you.

Mr. PITTS. Recognizes the gentleman from Louisiana, Dr. Cassidy, for 5 minutes for questions.

Dr. CASSIDY. I see in your testimony you are concerned regarding the tracking of drugs in order to detect counterfeiting. One of my concerns though, and which Dr. Woodcock agreed, if somebody is buying from an illegitimate online pharmacy, they are buying straight from an overseas provider, then really the absence of an RID or something similar, a unique identifier, would not provide any benefit. The person is going to open up their package and they are going to open it and they are not going to look to see, oh, my gosh, is there something tracking it? Would you agree with that?

Mr. COUKELL. I think it is important to note that there are both legitimate and illegitimate online pharmacies and many of our big retail chains operate online pharmacies. So if a person is obtaining drugs from the legitimate supply, whether they are going to a brick-and-mortar pharmacy or online—

Dr. CASSIDY. Well, I agree with that totally—

Mr. COUKELL [continuing]. Then it is difficult.

Dr. CASSIDY [continuing]. And I don't mean to interrupt; it is limited time.

Mr. COUKELL. But—

Dr. CASSIDY. In fact, that is my point. Right now, the consumer has limited ability to tell the difference between a legitimate and an illegitimate. And even though one of the things we can use to track counterfeits would be this unique ID system. Nonetheless, it still would not identify counterfeit drugs arriving in your mailbox from an illegitimate pharmacy.

Mr. COUKELL. That is correct.

Dr. CASSIDY. Yes. So now, that said, Ms. Radcliffe and Dr. Wheadon, I am very interested in these rare pediatric diseases. Your heart tugs, they affect so few, it is hard to get an adequate in for a clinical trial, and there is never going to be a major investment by a pharmaceutical company if it is based upon return, OK. I read your testimony regarding the bills we have to promote pediatrics. What ideas do you have in order to encourage research into cures for these terribly tragic but rare diseases? You see where I am going with that.

Ms. RADCLIFFE. This is an issue of extreme interest to many of our companies for the reason that you say. It tugs on the heartstrings when there are these very rare pediatric conditions and there are no cures for them. We have worked on this issue in a number of different ways. Specific to the issue at hand in this hearing today within the PDUFA agreement there is a provision for helping companies to move forward with drug development on rare conditions where FDA will have additional resources to hire expertise and to reach out to the community and gain input on how that may be done.

Additionally, we support—as I said in my both written and oral testimony—the Faster Access to Specialized Treatments Act, which seeks to expand accelerated approval in a way that would allow the

use of that pathway for more conditions by encouraging FDA to take advantage of modern tools, whether it is biomarkers, pharmacogenomics, predictive toxicology and so forth, and to expand these so that pathway to—

Dr. CASSIDY. Let me ask you because that seems as if those products would be a byproduct of research focused elsewhere. Does that make sense?

Ms. RADCLIFFE. In some cases, yes, but that may be a very effective way of ensuring that those products do get developed.

Dr. CASSIDY. Is there a way to encourage the pharmaceutical companies in a market-based approach to focus resources on a particular illness? You are more likely to get to your destination if you go there directly theoretically than if you just kind of as a, you know, circuitous route end up there.

Ms. RADCLIFFE. Right. That gets to a much broader discussion, I think, about the incentives that are available for research and development, whether it is R&D tax credits, whether it is the way the products are reimbursed and so forth, a very complicated decision that I think goes far beyond what FDA could accomplish. FDA, however, has a huge role in ensuring that companies have the information that they need to create drug development programs in rare disease which encounter challenges that are, honestly, not just related to the return that companies get—

Dr. CASSIDY. A friend of my who has such a child—so there is kind of a personal interest in mine—

Ms. RADCLIFFE. Yes.

Dr. CASSIDY [continuing]. He tells me that there is a bill being considered or proposed and if the company came up with such a drug for such a rare condition, they would get a transferrable sort of expedited review of any other drug. Now, would that be an effective way to do this or would that be—and I will open that up to the panel if anybody has a thought on this.

Ms. RADCLIFFE. Sure. We are aware of that legislation and we haven't taken a position on it. That mechanism has been tried in other settings and we certainly think that where such a mechanism could be put in place, it is useful to do so, but it hasn't proven so far to really be a major incentive for this type of work.

Dr. CASSIDY. Thank you. I yield back. Thank you.

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.

Mr. Coukell, I am going to ask you about antibiotics. I know that Pew has had a longstanding interest in making sure that we get more antibiotics, new antibiotics, so our arsenal is full, but I don't think we just want any antibiotics. We don't need two versions of the same antibiotics we already have. That would I am sure only serve to worsen the problem of antibiotic resistance. So I want to search your views on whether the language in the discussion draft for this hearing will achieve this goal.

The bill, as it is currently written, would grant exclusivity for any antibiotic to treat essentially any resistant bacterial pathogen. Is that approach adequate to ensure that we get only the antibiotics that we truly need? And if not, is there another approach

that you would suggest we take so that we can better target those drugs?

Mr. COUKELL. Thank you for that question, sir. I think the goal in the discussion draft is to make it more attractive for companies to be in the business of antibiotics. So that means they need predictability. We need to address the serious public health problem and we need to make sure that we are using taxpayer resources wisely. While we are on predictability, right now, the discussion draft has a list of bugs in it, and the question is if you get qualified early on as you do under the Orphan Drug Act as a qualified product, how does that carry through to you doing your clinical studies and coming to market? Bleach will kill resistant bugs; nobody would suggest it is a good drug. And so the question is, is there an established way to look at antibiotics and say here are the ones we need and here is how it would work through to market? And we think that looking at serious and life-threatening infections would be a very workable way to do it. It would address the public health need and provide great predictability.

Mr. WAXMAN. So target it in that way and not have it more general—

Mr. COUKELL. In some ways that is broader in the sense that you don't have to have activity against the resistant organism but you are tackling the public health aide, which is a treatment for a serious or life-threatening infection.

Mr. WAXMAN. OK. Now, the LPAD offers an approach that I think should be given serious consideration because it has a potential to get important new antibiotics into market more quickly than usually possible. However, when we are getting products to market more quickly based on more limited clinical data they usually require, it becomes that much more important that we are confident that they will be used only in the small populations for which the drug was approved.

With antibiotics, this concern is doubled. We must worry not only about patients receiving medications that could be dangerous to them because their safety has not been established in broader populations, we also need to act in a way that will preserve the efficacy of new antibiotics by using them only when truly necessary. Do you believe that the mechanism for limiting off-label use of antibiotics approved under LPAD will be effective in achieving both of these goals, and if not, do you have suggestions for additional mechanisms?

Mr. COUKELL. We think it is an interesting proposal. And let me make a couple of points about what we are thinking as we consider it. And we are still trying to understand how it would work. But first, it is attractive if you could have a faster pathway and then use the drugs only in patients that you couldn't treat with existing drugs. That would be good for public health and it would be good for the companies assuming there is a viable business model there. So one question is what does it take to get these drugs to market and get that particular designation?

And then the limited population part of the Limited Population Provision is how do we ensure that if they are coming with a higher risk or lower evidence that they are used the way we intend—and there is nothing in the statutory language that ensure that—

so the question is how would individual providers, how would payers, how would hospital formulary committees use these drugs and ensure that they were used only on label. And that is something that we are still trying to understand.

And then the other thing I think you would want to know is if you are approving drugs based on less evidence, do we have a mechanism of post-market surveillance so we can continue to learn as they are in clinical use?

Mr. WAXMAN. Well, what is your reaction to what is in the draft?

Mr. COUKELL. We are still studying. We think it is interesting, but as I say, we are trying to understand—

Mr. WAXMAN. You are still thinking but it needs to be refined in some way. You are trying to think it through?

Mr. COUKELL. Trying to think it through.

Mr. WAXMAN. Is that it? OK. Well, we are, too, and so we would appreciate your suggestions.

Mr. Chairman, I am going to yield back my time. Thank you.

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

Mr. SHIMKUS. Thank you, Mr. Chairman.

And it may have been noted before but I see Dr. Shuren is still in the committee room. Thank you for being here. This is important. Even my follow-up is going to be on the, again, working on the IDEs and the 510(k) a little bit more. Most of my questions will be directed to Mr. Levitt, but I do appreciate you being here. I did like Dr. Woodcock's statement Congress needs to define a problem that we want to address, and we really do think there is a problem with the change in the process in these two areas.

So with that, Mr. Levitt, you said in the explanation to the chairman's question about—kind of explain the Investigative Device Exemption, safety and protocol were the two primary issues. And then the FDA's change in the processing, that it has to be good enough for final approval. Are there benefits to going through the Investigational Device Exemption process even though you might not eventually get to a final approval in the process? Are there positives going through this process?

Mr. LEVITT. Well, I think there are positives any time you are learning new information in a structured setting under informed consent of course about the performance of new devices or improved devices both for safety and for effectiveness. Very often, a company may want to try something and if it is not working have a small trial and learn that quickly and pursue another direction. Or they may want to proceed in a more robust way because they have greater confidence. So I think there is value in any clinical study that is safe and that has a bona fide research protocol to greater learning.

Mr. SHIMKUS. So the FDA's change in focus—I do think there are benefits from going through—if you meet the two criteria of safety and bona fide protocol—and that the information you learn may help you or may help the sector move in a more robust path forward or to change course and start anew. That is summarizing what you said?

Mr. LEVITT. Yes.

Mr. SHIMKUS. I am not going to go over the issue of what is the legal law and what is the—what was the other thing I had here on the Administrative Procedures Act? And there are some, I think, legal concerns with the change without it being bona fide. You might have some experience in your legal background and your other history with that, but I think I addressed that enough.

On the 510(k) process, can you walk us through what currently happens when a company makes a modification to existing 510(k)?

Mr. LEVITT. Yes. When companies often make changes to their devices, FDA has a flowchart to help companies walk through is this a significant change affecting safety and effectiveness? If it is, then the company submits a new 510(k). If it isn't, the company documents what their decision and a basis is. They make the change and they move on. That information is available to FDA during an FDA inspection so there is still transparency.

Mr. SHIMKUS. So have you heard—obviously, from the sector now that you are representing—the concern that with the changed rules, there may be a projected backlog of 300 to 500 percent and that this is harmful to the process, not helpful?

Mr. LEVITT. Yes, I have certainly heard that. I mean what Dr. Shuren testified this morning, if I heard him correctly, was that FDA really was just trying to affect a little gray zone, a small number around the margin. But as companies went back and applied the examples, companies saying oh, no. You, FDA, really missed the mark. This would result in just a flood of new 510(k)s where there really is not a significant change. But the examples that FDA gave led them to believe they would have to submit this. So there is clearly a gap between what FDA intended and how the industry is perceiving it. And I think Dr. Shuren testified he recognized that and he needs to address that.

Mr. SHIMKUS. I appreciate you all being here today and, Dr. Shuren, that is why I appreciate you remaining in the committee room because, you know, the other issue is resources, which we can agree to disagree. But I do think we want to improve the system. This is our one opportunity to do that.

And my time is expired, Mr. Chairman. Thank you.

Mr. PITTS. The chair thanks the gentleman.

That concludes the questioning. I would like to thank the panel. This has been an extremely valuable hearing, very important information.

I have a unanimous consent request to enter into the record statements from the National Alliance on Mental Illness and the California Healthcare Institute. That has been shared without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. I remind Members that they have 10 business days to submit questions for the record, and I ask all witnesses to respond to questions promptly. Members should submit their questions by the close of business on Wednesday, May the 2nd.

Without objection, the subcommittee is adjourned.

[Whereupon, at 2:44 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]



**STATEMENT TO THE HOUSE ENERGY & COMMERCE
COMMITTEE, SUBCOMMITTEE ON HEALTH ON THE PDUFA V
TECHNICAL AGREEMENT**

February 1, 2012

Chairman Pitts, Ranking Member Pallone and members of the Subcommittee, on behalf of the National Alliance on Mental Illness (NAMI), I am pleased offer our views on the Prescription Drug User Fee Act (PDUFA) V Technical Agreement. NAMI is the nation's largest grassroots mental health organization dedicated to building better lives for the millions of Americans affected by mental illness. NAMI advocates for access to services, treatment, supports and research and is steadfast in its commitment to raising awareness and building a community of hope for all those in need.

PDUFA & Access to Innovative Treatments for Serious Mental Illness

NAMI has always placed the highest priority on expanding access to newer and more effective treatments for serious mental illness. The reality is that all of the current treatments for serious mental illness are palliative in nature and are designed to alleviate symptoms (both positive and negative) and improve functioning. What is desperately needed are a new generation of treatments and therapies that genuinely change the course of disorders such as schizophrenia and bipolar disorder and allow for complete recovery. At NAMI, we refer to this as moving to cure. We are not there yet, but cutting edge research on genetics and biomarkers are demonstrating enormous promise. As this research moves forward, it must be accompanied by a modern and efficient PDUFA process at the FDA.

NAMI also believes that incremental improvements to the treatments we have today for serious mental illness are also critically important for many people living with these disorders. For example, new compounds that can demonstrate innovation with respect to negative symptoms or cognition and executive functioning in schizophrenia can be critical tools in helping a patient attain greater independence, employment or community integration. Likewise, a new compound that offers incremental improvements with respect to a particular side effect profile can make a vast difference in helping with treatment adherence for many patients. Improvements to PDUFA can and should take into account this incremental progress that can genuinely advance treatment for people living with serious mental illness.

NAMI Supports the PDUFA V Technical Agreement

NAMI was pleased to take part in the Patient and Consumer Stakeholder Group that has worked with the FDA throughout this PDUFA V process. We are grateful for the time and resources that the leadership at CDER has put into this process over the past 18

months. NAMI is now pleased to go on record in support of the major provisions in this Technical Agreement.

1) Performance Goals

NAMI strongly supports the new performance goals that will increase drug review efficiency and predictability. These performance goals can and should result in more consistent and transparent drug reviews. NAMI is pleased that the provisions in this Agreement will more clearly discern how efficacy and safety parameters are balanced as part of the FDA's risk-benefit analysis. We also hope that the new performance goals will help ensure that the FDA's regulatory decisions are based on the best available scientific methods. NAMI also supports the inclusion of measures to ensure better communication with sponsors to support more efficient review.

2) Enhanced Benefit Risk Assessment

As noted above, NAMI is pleased that this Agreement will bring greater transparency to the benefit-risk assessments FDA makes that too many of us has often been opaque and difficult to understand, especially when decisions have been made across multiple divisions and offices. The improvements in this Agreement should bring more transparency to this process. Increasing the public's understanding of this process should also help improve public confidence in the agency's decisions.

3) Electronic Submissions and Standardization of Application Data

During the work of the Stakeholders Group, we were stunned to learn that applications for NMEs often involved submission of large volumes of data in the form of paper records stored in dozens of boxes with no system or process for FDA reviewers to efficiently examine the results of randomized clinical trials that took place at multiple sites. This new requirement for electronic submission and standardization of application is long overdue. It is central to making the overall review process more timely, efficient and less costly.

4) Independent Review of PDUFA Performance Goals

NAMI strongly supports the provisions in the Agreement on enhanced independent review of performance goals. In order to ensure that the PDUFA V goals are met, there must be an independent third party assessment. NAMI is pleased that this assessment would be required both in 2015 and 2017, with full opportunity to all stakeholders to offer comments on the assessment.

5) Regulatory Science Improvements

NAMI supports the new investments in the Agreement aimed at improvements on pharmacogenomics and biomarkers. The application of qualified biomarkers has enormous potential to accelerate drug development by helping to identify and predict

which patient will respond to a particular medication. Biomarkers offer particular promise with respect to treatment for schizophrenia. Under the Agreement, FDA will be able to access new resources to augment its clinical pharmacology and statistical capacity to better address submissions that propose to utilize biomarkers or pharmacogenomics. NAMI also supports the provisions in the Agreement that will allow FDA to support the advancement and validation of meta-analysis to improve drug safety decision-making.

6) Patient Reported Outcomes (PROs)

PROs can be critical endpoints for measuring the benefit-risk profile of a new treatment from the patient's perspective. NAMI is pleased that the Agreement includes advancement and validation of PROs. This should help improve the agency's clinical and statistical capacity to address submissions involving PROs and other end point assessment tools. NAMI is also supportive of the requirement for FDA to hold a public meeting to examine standards for PRO qualification and development.

7) Patient Safety Improvements, REMS & Sentinel

NAMI supports the improvements in PDUFA V to enhance FDA's existing safety system. The improvement to REMS and Sentinel are vital to this ongoing effort to ensure patient safety. For example, improvements will allow FDA to test the feasibility of using Sentinel for evaluating drug safety issues that may require some form of regulatory action such as a label change. This should help accelerate the time it takes to understand an emerging safety issue. Likewise, the requirement in the Agreement for standardizing REMS is a needed improvement. This should better integrate REMS-related activities into FDA's review process and the larger health care system with the goal of reducing the burden of REMS on patients and providers.

8) Conflict of Interest in FDA Advisory Panels

While this issue is not a part of the formal PDUFA V Technical Agreement, NAMI would like to call attention to a recent letter signed by NAMI and more than a dozen colleague health and patient advocacy organizations calling attention to deficiencies in FDA's current process for assessing conflicts of interests among scientists and researchers serving on agency advisory panels. NAMI agrees that protections must be in place when individuals are appointed to positions where their own financial interests might influence their service on agency advisory panels. At the same time, current conflict of interest statutes that apply to the FDA have resulted in a system that is out of balance to the point that conflict avoidance is the primary driver of who serves on advisory panels, regardless of the extent of the conflict, the uniqueness of their expertise, or the government's need for their services.

The result is that many of the agency's advisory panels, including the Psychopharmacologic Drugs Advisory Committee, are routinely deprived of the most experienced and knowledgeable experts in a particular therapeutic area. NAMI

therefore joins our colleagues in supporting the elimination of the e additional conflicts of interest restrictions that apply only to the FDA. In fact, the existing provisions in the Federal Advisory Committee Act and the Ethics in Government Act of 1978 can serve as an adequate safeguard against conflicts of interest, while still allowing those with the necessary expertise and perspective to serve on these very important advisory committees.

Respectfully Submitted,

Andrew Sperling, Director of Legislative Advocacy
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Statement of the
California Healthcare Institute (CHI)

House Energy & Commerce Committee
Subcommittee on Health
Legislative Hearing on
“FDA User Fees 2012: How Innovation Helps Patients and Jobs”

Wednesday, April 18, 2012

The California Healthcare Institute (CHI), the statewide public policy association representing California’s diverse life sciences research and development community, appreciates the opportunity to address the importance of FDA user fee reauthorization to improvements in Agency performance, biomedical investment and innovation, patient care and economic growth.

The Food and Drug Administration (FDA) and its regulatory policies profoundly influence the current state and future strength of the U.S. biopharmaceutical and medical technology industries. Indeed, a strong, science-based Agency and efficient, predictable and transparent regulatory processes are essential elements of the biomedical innovation ecosystem, which today employs nearly 270,000 Californians across our state.

In recent years, however, the environment for medical innovation has deteriorated. This is partly the result of the financial crisis and ensuing Great Recession, which sharply reduced investment capital. But the most critical factor has been the FDA’s recent regulatory policies and activities, which have exemplified President Obama’s critique of a system whose “rules have gotten out of balance, placing unreasonable burdens on business — burdens that have stifled innovation and have had a chilling effect on growth and jobs.”¹

That is why reauthorization of the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee Act (MDUFA) is so important. Both agreements represent the next step in an ongoing partnership between the FDA and industry. And importantly, the agreements are highly focused, providing the FDA significant resources and improving processes and performance goals to re-center the Agency toward its primary missions of protecting and *promoting* public health.

For example, both PDUFA and MDUFA:

- **Improve FDA-Industry Communications Processes** – Communication between the FDA and drug and device developers is critical. The earlier questions can be raised, and answers provided, the more likely that the review process won’t be affected by late-breaking or unexpected complications. Both agreements

¹ “Toward a 21st-Century Regulatory System,” Wall Street Journal, Jan. 18, 2011.

include provisions to ensure the FDA communicates with new product sponsors at all stages of the development and review process, improving predictability and transparency.

The PDUFA agreement:

- Enhances the Agency's Benefit-Risk Assessment – Everyone – the FDA, industry, patients and the public – would gain from an improved understanding and appreciation of the benefit-risk balance. No medicine or medical technology is risk-free, yet the expectation of the public and others is often just that. The PDUFA agreement will support the development of benefit-risk assessment tools to help reviewers better evaluate new medicines, including documentation of drug benefits -- such as if it meets an unmet medical need -- as part of the approval process.

And the MDUFA agreement:

- Strengthens FDA Performance and Accountability – Prior device review performance reports were based upon the “FDA clock,” which often frustrated industry by allowing the Agency to “stop the clock” one or more times during product review while still meeting technical Agency performance requirements. Under the MDUFA agreement, performance will be reported more sensibly, improving efficiency, transparency and consistency, by measuring average total review time --from the time of submission to the time the Agency makes a decision.

These and other provisions included in the Energy & Commerce Committee user fee reauthorization discussion draft demonstrate that, working together, Congress, the FDA, industry and other stakeholders can maintain the high standards of safety and effectiveness that physicians, patients and their families expect while also improving the consistency, predictability and transparency of FDA product review processes and management. The result will lead to an improved Agency, improvements in the care of patients in need, and improvements in the U.S. biomedical innovation ecosystem that help drive investment, growth and job creation in the increasingly competitive 21st century global economy.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

OCT 18 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 Food and Drug Administration (FDA or the Agency) the opportunity to testify at the April 18, 2012, hearing entitled "FDA User Fees 2012: How Innovation Helps Patients and Jobs," at which Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health, and Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, testified. This letter provides responses for the record posed by certain Members of the Committee, which we received on July 27, 2012.

If you have further questions please let us know.

Sincerely,

A handwritten signature in cursive script that reads "J. Ireland".

Jeanne Ireland
Associate Commissioner
for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce

Page 2 – The Honorable Joseph R. Pitts

We have restated the questions below in bold, followed by our responses.

The Honorable Brian Bilbray

The Committee understands that the FDA’s General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee convened a March 2010 hearing to review the classification of indoor tanning beds. The panel voted unanimously that a Class I designation did not reflect the risks associated with the device and recommended that the classification of tanning devices be changed. Please update the Committee on the actions taken by FDA on reclassifying these devices since the panel vote.

By way of background, FDA regulates sunlamps, tanning beds and booths, and portable home units for general use as Class I medical devices. Ultraviolet (UV) lamps for dermatologic purposes are regulated as Class II devices. FDA also regulates these products under the Electronic Product Radiation Control Act provisions, section 532 et seq., of the Federal Food, Drug, and Cosmetic Act. In addition to complying with requirements applicable to medical devices, tanning devices must also comply with Title 21 *Code of Federal Regulations* (CFR) section 1040.20—Sunlamp products and ultraviolet lamps intended for use in sunlamp products (the sunlamp products performance standard). This regulation contains requirements for all UV tanning lamps, which include requirements regarding warning labels, limits on the ratio of UV-C to UV-B wavelengths, use of protective eye wear, and timer systems.

FDA has been actively evaluating its regulation of indoor tanning devices amid rising concern by the Agency, the medical and scientific communities, the public, and Congress about the safety of their uses. At the same time, we have issued Warning Letters to manufacturers who have been in violation of existing regulatory requirements and worked with the Indoor Tanning Association to share helpful information with industry.

As you note, FDA held an advisory committee meeting in March 2010 to seek independent, professional expertise and advice on regulatory issues related to tanning devices. The panel discussed a variety of variables that would affect the reasonable assurance of safety and effectiveness for UV lamps for tanning, including user age, family history and education, user information prior to use, irradiance wavelength, FDA device classification, registry programs funded by user fees, and training of tanning bed operators. The Agency reviewed all of the comments received at that meeting, as well as the information in the scientific literature. There was a unanimous conclusion by the panel that these products should not be Class I devices. The Panel was split, however, between recommending that tanning devices be Class III (acknowledging the impracticality of requiring premarket approval submissions) and recommending that these devices be Class II (citing age, skin type, and medications as potential special controls).

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FDA has evaluated the information relayed at this panel meeting and is working to ensure that any regulatory action taken by the Agency effectively addresses the risks associated with tanning devices. FDA convened an Agency expert group to draft regulations to address the recommendations of the 2010 advisory committee in conjunction with consideration of information gleaned from the additional efforts mentioned below. The Agency currently is working on draft regulations and accompanying guidance. We recognize that this is an important issue, and we are working diligently to protect public health.

In addition to FDA's work to address the 2010 advisory committee recommendations, the Agency has taken other actions to review the safety of these devices and educate consumers about the risks associated with tanning.

Prior to the March 2010 advisory panel meeting, FDA conducted consumer testing to evaluate the effectiveness of indoor tanning device warning labels. Based on this testing, FDA determined that changes to the language, format, and positioning of these labels may more effectively communicate the risks of these devices.

FDA also engaged in joint studies with the National Cancer Institute^{1,2,3} and found that UV exposures typically provided by sunlamp products are excessive, and that comparable cosmetic effects can be produced with exposures that are only one-third or even one-fourth the levels of UV exposure currently. FDA is considering whether changes to the performance standard might be warranted for sunlamp products from these findings.

Finally, FDA wants consumers to be aware of the health risks posed by UV radiation from tanning devices. FDA posts extensive information on the health risks of tanning on its "Tanning" webpage, located at <http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/Tanning/default.htm>. The website includes links to related information posted by the Centers for Disease Control and Prevention, the National Institutes of Health, and the World Health Organization. FDA held a webinar in April 2012 on the risks of UV radiation, posted a video, and published a lesson plan for health educators to help students understand the risks associated with tanning and UV exposure.

¹Reduction of the UV burden to indoor tanners through new exposure schedules: a pilot study. Miller SA, Coelho SG, Zmudzka BZ, et al., *Photodermatol.Photoimmunol.Photomed.* 2006; 22: 59-66.

²Dynamics of pigmentation induction by repeated ultraviolet exposures: dose, dose interval and ultraviolet spectrum dependence. Miller SA, Coelho SG, Zmudzka BZ, Bushar HF, Yamaguchi Y, Hearing VJ, and Beer JZ, *British Journal of Dermatology*, 2008; 159: 921-930.

³Cyclobutane pyrimidine dimer formation and p53 production in human skin after repeated UV irradiation. Yamaguchi Y, Coelho SG, Zmudzka BZ, et al., *Exp. Dermatol.* 2008; 17: 916-24.

The Honorable Edolphus Towns

- 1. Antibiotics are unique. We must both provide incentives to encourage R&D and discourage resistance which is inevitable.**

The Infectious Diseases Society of America and others have called for a new antibiotic pathway called the Limited Population Antibacterial Drug (LPAD) pathway. I understand this mechanism will allow FDA to approve high priority antibiotics that are studied in smaller, less expensive clinical trials than normally required, but would limit its marketing to patients with the most serious infections. The concept is similar to the Orphan Drug Program, which apparently does not apply to this type of anti-infective products.

What are your thoughts regarding this proposal? Would it help get needed antibiotics to patients with serious life-threatening bacterial infections with no other options?

The LPAD proposal from the Infectious Diseases Society of America (IDSA) seeks to provide an important new tool for the development of urgently needed antibacterial therapies to treat patients with serious infections who currently lack satisfactory treatment options. An LPAD development program is envisioned to be smaller than a traditional development program, with the intent to encourage the rapid development of antibacterial products to meet pressing unmet medical needs in smaller populations (e.g., those with serious infections due to multidrug-resistant organisms). It is important to recognize that a smaller development program also would likely result in greater uncertainty at the time of marketing approval regarding the characterization of the safety and efficacy of an LPAD drug; however, the drug may have an acceptable benefit-risk profile in a limited population with a serious disease. In addition, the LPAD designation could serve as an important signal to physicians, patients, and the health care community that, based on the available evidence, FDA considers the drug to be in a special category requiring more judicious and carefully managed use. That is, it should only be used in the patient populations where the risk-benefit profile is appropriate because the patients have a serious or life-threatening infection and limited alternative therapies, and should be used prudently to avoid accelerating the development of resistance to the LPAD drug.

The Orphan Drug Act provides a different framework for encouraging the drug development of treatments for rare diseases and conditions. It provides financial incentives to reduce the costs and potentially increase the value of developing drugs for rare diseases and conditions. These orphan incentives include grants, tax credits, a waiver of marketing application user fee, and potential market exclusivity upon approval. To be eligible for the incentives, sponsors must request and obtain "orphan designation" for their products prior to submitting marketing applications for these products. Anti-infective products could also be eligible to receive orphan drug designation and these associated incentives if they meet the requirements set forth in

the Orphan Drug Act and its implementing regulations; however, this is often not the case.

- 2. I understand that the sarcoma patient community has submitted a petition to the FDA regarding the upcoming regulatory action for the therapy pazopanib, a treatment for metastatic sarcoma. For rare disease patient populations, there exists a unique risk/benefit balance that must be taken into account.**

Has the FDA taken into account the input, preferences, and needs of the sarcoma patient community? Has FDA engaged in a dialogue with the affected patient population?

In April 2012, FDA approved the oral medication Votrient (pazopanib hydrochloride) for the treatment of patients with advanced soft tissue sarcoma who have received prior treatment with chemotherapy.

FDA Office of Special Health Issues (OSHI) staff have been in contact with patient advocacy organizations that collectively represent patients with sarcoma to hear their concerns and assure them that FDA is aware of the need for effective therapies for this patient population. OSHI also has three patient representatives in their patient representative program who represent the sarcoma patient community at advisory committee meetings. On March 20, 2012, the Oncologic Drugs Advisory Committee (ODAC) convened to discuss pazopanib, and one of the three patient representatives served on the panel. FDA also receives input from the sarcoma advocacy community via Special Government Employees with expertise in sarcoma, who serve as temporary voting members of the ODAC.

FDA's Center for Drug Evaluation and Research's Office of Hematology and Oncology Products routinely engages the oncology community regarding the needs of patients with sarcoma by presenting data at the American Society of Clinical Oncology's annual meetings. FDA staff also attend annual scientific meetings, such as the Connective Tissue Oncology Society and the Children's Oncology Group, to stay up to date on new developments in the field.

FDA has been developing an enhanced, structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency's drug regulatory decision-making. Part of FDA's decision-making lies in thinking about the context of the decision—an understanding of the condition treated and the unmet medical need. Patients who live with a disease have a direct stake in the outcome of drug review. The FDA drug review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and the potential gaps or limitations in available treatments in a therapeutic area. The most recent Prescription Drug User Fee Act enhancements include expanded implementation of FDA's benefit-risk framework in the drug review process, including holding public workshops to discuss the

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application of frameworks for considering benefits and risks that are most appropriate for the regulatory setting.

Please be assured that FDA is very much aware of, and sympathetic to, the desperate situation of patients with illnesses such as sarcoma, for whom there are limited or no available alternative therapies. The Agency is committed to providing timely access to potentially useful medical treatments for seriously ill patients, as well as working for speedy approval of new drug and biological products while maintaining the scientifically based safety and efficacy standards mandated by Congress.

Concerning your inquiry about the submission of a Citizen Petition regarding pazopanib hydrochloride, at this time, FDA does not have any evidence that a Citizen Petition was submitted and received by the Division of Dockets Management. Title 21 CFR 10.20 (f) provides that all petitions are to be mailed or hand delivered in person to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. If this process was not followed, it will cause a delay in the receipt of the petition by the Division of Dockets Management and the subsequent assignment of a docket number.