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FDA USER FEE AGREEMENTS: STRENGTHENING FDA AND THE MEDICAL PRODUCTS INDUSTRY FOR THE BENEFIT OF PATIENTS

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TWELFTH CONGRESS

SECOND SESSION

ON

EXAMINING FOOD AND DRUG ADMINISTRATION (FDA) USER FEE AGREEMENTS, FOCUSING ON STRENGTHENING FDA AND THE MEDICAL PRODUCTS INDUSTRY FOR THE BENEFIT OF PATIENTS

MARCH 29, 2012

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C O N T E N T S

STATEMENTS

THURSDAY, MARCH 29, 2012

FDA USER FEE AGREEMENTS: STRENGTHENING FDA AND THE MEDICAL PRODUCTS INDUSTRY FOR THE BENEFIT OF PATIENTS

THURSDAY, MARCH 29, 2012

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

The committee met, pursuant to notice, at 10:06 a.m. in Room SH–216, Hart Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Mikulski, Murray, Hagan, Merkley, Franken, Bennet, Whitehouse, Blumenthal, Enzi, Burr, Isakson, and Roberts.

OPENING STATEMENT OF SENATOR HARKIN

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

Last summer, FDA Commissioner Margaret Hamburg testified before this committee describing the history and importance of the user fee agreements between the FDA and the industries that it regulates. She detailed the impact that user fees had on FDA's ability to ensure that new medical products get to American patients as quickly as possible.

Since then, we have had hearings on a number of policy areas relating to the FDA, including supply chain security, medical devices, and drug shortages. While we were engaged in those hearings, and a lot of related behind the scenes work, the FDA and industry were negotiating and finalizing this year's user fee agreements.

Today, in our last hearing of this reauthorization process, we turn the spotlight to those agreements. We will focus on how the Prescription Drug User Fee Agreement, or as it is known, PDUFA, how it will improve FDA's review of the most novel drug products, and enhance the agency's commitment to regulatory science.

We will discuss the exciting new Generic Drug User Fee Agreement—wouldn't you know it—called GDUFA, which is expected to slash review times to a third of current levels, drastically improving the speed with which generic products are made available to patients.

We will also hear about the new Biosimilars User Fee Agreement—ready for this one—BsUFA, which will shepherd the nascent generic biologics industry as it grows and matures.

On the device side, we will discuss the importance of the hard-fought Medical Device User Fee Agreement—one more time—MDUFA, to improving the device review process while stimulating safety standards.

In our first panel, Dr. Janet Woodcock and Dr. Jeff Shuren, the Directors of FDA's Drug and Device Centers, respectively, will discuss the critical role user fees play in helping them ensure that medical products are safe and effective, and that they reach patients as quickly as possible.

In our second panel, Dr. David Wheadon from PhRMA, Miss Sara Radcliffe from BIO, and Mr. David Gaugh from GPhA will discuss the drug user fee agreements.

The device industry, including members of the Medical Device Manufacturers Association, and the Medical Imaging Technology Association will be represented by Dr. David Nexon of AdvaMed.

Finally, Mr. Allan Coukell will join us, from The Pew Foundation, to explain the benefits these agreements will have for patients and consumers.

The testimony of today's witnesses will reflect strong agreement on the following points: these agreements were carefully negotiated and it is essential that we pass them. They are critical to FDA's ability to do its job, to the medical products industry's ability to survive these challenging economic times, and most importantly to the patients who are the primary beneficiaries of this longstanding and valuable collaboration between the FDA and the industry.

After months of negotiation, the FDA and industry have crafted a win-win agreement that they stand behind, and they have done their job well. Now it is time for us to do ours. If we fail to authorize these agreements on time, the FDA will have to fire nearly 2,000 from its staff. Without adequate staff, review applications of the drug and device approval process will grind to an unacceptably low and slow pace. Patients whose health and lives depend on new medical treatments will suffer the devastating consequences. We cannot let that happen.

We cannot let policy disagreements, or Presidential election year politics, or other politics keep us from doing our part to translate into legislation the arrangement and the deal that the FDA and the industry have struck for the benefit of American patients.

As we have from the beginning of this process, Senator Enzi and I, and other members of this committee from both sides of the aisle, are continuing to work together to clear the path to authorization of the agreements that we will hear about today.

With that, I will turn to our Ranking Member, Senator Enzi.

OPENING STATEMENT OF SENATOR ENZI

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

I also want to reiterate the comment that you just made about the cooperation between both sides and all of the people that have been involved and invested in getting this done. We know that it has to be done by September, and I think we are actually ahead of schedule on that, and hopefully we can stay that way. There has been good cooperation from everyone; still a few things to consider.

The subject of today's hearing is the Food and Drug Administration's human medical product user fees; all of the "UFA's" today.

The first such agreement was enacted in 1992. It allowed FDA to collect certain agreed upon user fees from drug manufacturers in exchange for more timely, predictable, premarket review. It decreased review times and increased patient access to medicines. User fees are important to America's patients, jobs, and innovation. User fees currently support about 60 percent of the drug center's workforce, or about 20 percent of the device center's workforce.

The current user fee agreements expire on September 30th of this year, 6 months from now. If they are not timely reauthorized, the FDA must layoff approximately 2,000 employees. That would derail the agency's premarket review programs. It would threaten the biomedical industry jobs. It would limit patient access to therapies and America's global leadership in biomedical innovation.

I am committed to enacting user fee legislation in a timely manner. I expect that all our witnesses today representing the administration, industry, and patient consumer groups alike share that commitment. They will brief us on the content and merits of the proposed agreements.

The agreements contain important policies that will ultimately help patients. The proposed prescription drug user fee agreement would factor a better understanding of the patient perspective into benefit-risk decisions. It would also improve Risk Evaluation and Mitigation Strategies, or REMS.

REMS enacted in 2007 were intended to let the FDA ensure that the benefits of a drug or biological product outweigh its risks, but implementation of the law produced a delay and confusion. The proposed agreement should go a long way toward fixing those problems. For instance, by standardizing the process and clarifying that the medication guides are not part of REMS.

The proposed Medical Device User Agreement will help FDA hire and train more reviewers, managers, and technical writers. It will also improve the predictability of the pre-submission process, and ensure that no submission is left behind.

The proposed Generic Drug User Fee Agreement will help the FDA inspect more foreign establishments, and attack a large backlog of applications. These new user fees will also help FDA tackle the problem of drug shortages, providing the resources needed to expedite the review and the approval of more generic drugs.

The proposed Biosimilar User Fee Agreement will help get a biosimilar program up and running, with measures to prevent medication errors, resolve disputes, and authorize special protocol assessments.

Today, the HELP committee will assess the proposed user fee agreements to make sure they will advance the public health. We need to make sure the policy is right. At the same time, we also need to enact user fee legislation in a timely manner. Patients, jobs, and innovation depend on it.

Toward that end, the HELP committee plans to mark up one bill containing all four user fee agreements, and a small number of bipartisan consensus policy riders will face several obstacles that will make it difficult to enact these policies. Many outside forces, in some cases extraneous to FDA issues, all have the potential to de-

rail our process, but the bill will need very broad bipartisan support to pass the Senate.

I would encourage stakeholders to keep the big picture in mind as they contemplate trying to include proposals that could add cost, complexity, and/or controversy to the bill. We can only succeed if we work together for the greater good.

On that note, I want to point out that the device under director Jeff Shuren and AdvaMed senior executive vice president David Nexon are both here today advocating for the proposed medical device user fee. The negotiations concerning these agreements were contentious, but in the end, through hard work and compromise, they reached agreement.

In short, the FDA, industry, and the stakeholders have done their job. Now it is time for us to do our jobs and to get a bill done.

I thank Chairman Harkin for his leadership, commitment, and courtesy. I thank the witnesses for coming today, and I look forward to their testimony.

The CHAIRMAN. Thank you very much, Senator Enzi.

Now we will turn to our first panel. Our first panel will be Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration. In this position, Dr. Woodcock ensures that safe and effective drugs are available to address public health needs.

Dr. Woodcock is no stranger to this committee. I was just reading that Dr. Woodcock joined the FDA in 1986, has held various leadership positions within the Office of the Commissioner FDA, including Deputy Commissioner and Chief Medical Officer, Deputy Commissioner of Operations, and Chief Operating Officer and Director of the Critical Path programs.

We also have Dr. Jeff Shuren. He has been with FDA, I think since 1998, if I am not mistaken—is the Director of the Center for Devices and Radiological Health at FDA, and previously served as Acting Center Director. He has held various policy and planning positions within FDA from 1998 to the present time.

Dr. Shuren received both his B.S. and M.D. degrees from Northwestern under its honors program in medical education; his J.D. from the University of Michigan Law School. I noted that Dr. Woodcock, you received your M.D. from Northwestern University. Is this some kind of ganging up by Northwestern Medical School or something?

But welcome, both of you. Thank you for your service to our country. Your statements will be made a part of the record in their entirety, and I ask if you could sum them up within several minutes.

Dr. Woodcock, welcome. Please proceed.

STATEMENT OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. WOODCOCK. Thank you, Mr. Chairman.

I would like to thank you and the members of the committee for the opportunity to testify about the three drug user fee proposals now before you for consideration. Included is a proposal for reauthorization of PDUFA, and recommendation for two new user fee

programs: a groundbreaking program to support the generic drug review process, and a program to support the new biosimilars review activities.

Each of these proposals was negotiated with stakeholders, including a transparent process that provided multiple opportunities for public input. We feel that, taken together, they will support a robust drug regulatory program that will both encourage innovation and ensure that the American public has continued access to high quality, safe, and effective medicines. I would like to briefly describe each of these user fee programs.

To start with PDUFA, Congress instituted this program because patients in the United States were not getting access to new medicines as quickly as people in other parts of the world. This problem was known as "the drug lag," and it was particularly severe in the 1980s. In that decade, only about 10 percent of new medicines reached U.S. patients first.

PDUFA was started by Congress in 1992 and quickly improved the availability of new medicines. I am a rheumatologist, a doctor who treats autoimmune diseases and arthritis, and I can attest to the revolution in therapy that has occurred since the start of PDUFA. Diseases that were crippling now have effective treatments that allow our patients to lead full lives.

Recently, I was on an airplane and my seat mate showed me pictures of her garden that she maintained herself. Ten years ago, she had been in a nursing home, confined to a nursing home with crippling autoimmune disease. She was started on one of the new therapies and now is active and leads a full life.

Since the start of PDUFA, increasing numbers of new medicines have been available first in the United States. Currently, we lead all other countries in introduction of new therapies. But every 5 years, the user fee program must be reauthorized and each cycle has brought new enhancements to the program.

Recently, there has been a focus on improving drug safety and successful innovations such as our Sentinel Initiative have resulted from this.

For this cycle of PDUFA renegotiation, Congress directed us to conduct a very open and inclusive process with significant public stakeholder participation. We have done that, and we believe that was wise direction on the part of Congress, and the outcomes of the negotiation have improved as a result of this participation.

The drug development enterprise, though, that brings new therapies to patients is in a very different place than previous PDUFA negotiations. Drug developers face many of the problems of other industries due to the economic downturn. But more significantly, there is a severe productivity problem worldwide in which an ever increasing R&D investment is producing even fewer new drugs than before. It is no exaggeration to say this industry is in crisis.

At the same time, the scientific opportunities have never been greater, and I can tell you it is incredibly frustrating as a physician to see the expansion of biomedical knowledge, and at the same time to watch the struggles and repeated failures in developing new medicines.

Despite these serious problems, we think we may be seeing a turning point. Last year, we approved a very high number of new

medicines and this year we have approved, this calendar year, eight novel medicines so far and many of them will make a significant difference for patients. It is critical that the regulatory system be able to change, and adapt, and keep bringing this innovation to the public.

Through this process, we have developed a set of recommendations as laid out in my written testimony. These include new steps to incorporate these scientific advances into our regulatory process. To put the patient in the center of drug development by many patient-centered activities that are going to be supported by the new process, and to further enhance drug safety.

The second proposal is for a groundbreaking Generic Drug User Fee. This program has two elements, one establishing a timely predictable process for review of generic drug applications, and establishing a worldwide level playing field for manufacturers of generic drugs and their active ingredients, so American consumers can receive the same assurance of quality no matter where the drug is sourced from.

Finally, the user fee proposed are for the new biosimilars program, which is also a groundbreaking program established by Congress. This is intended to support implementation of this landmark legislation. Since there is no existing biosimilars industry in the United States, FDA worked with a wide range of stakeholders in crafting our proposal.

The program differs from others in that fees are going to be paid during drug development to assist in providing advice because it is not known how to develop biosimilars for the U.S. market.

In sum, these proposals will provide robust support for essential drug regulatory activities in the United States, and I look forward to answering your questions about them.

[The prepared statement of Dr. Woodcock follows:]

PREPARED STATEMENT OF JANET WOODCOCK, M.D.

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 DUFA–V, as well as the negotiated recommendations for a generic drug user fee program and a biosimilar user fee program.

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 PDUFA, which provided

[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 timeframe. 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.

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 timeframe. 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. 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 fiscal year 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 fiscal year 2011, FDA approved 35 new, groundbreaking medicines, including two treatments for hepatitis C, a drug for late-stage prostate cancer, the first drug for Hodgkin's lymphoma in 30 years, and the first drug for lupus in 50 years. This was the second highest number of annual approvals in the past 10 years, surpassed only by 2009. Of the 35 innovative drugs approved in fiscal year 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 6 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 fiscal year 2011, 24 (almost 70 percent) were approved by FDA before any other regulatory agency in the world, including the European Medicines Agency. Of 57 novel drugs approved by both FDA and the EU between 2006 and 2010, 43 (75 percent) were approved first in the United States.

Figure 1 below shows that since the late 1990's, 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.

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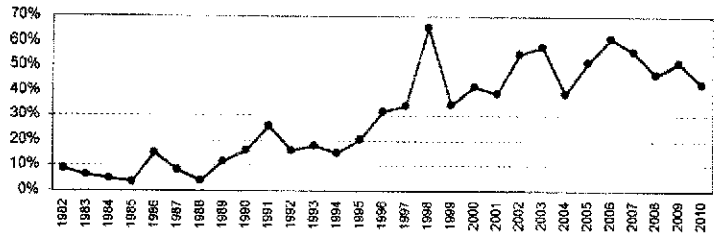
[2] Milne, Christopher-Paul (2010). *PDUFA and the Mission to Both Protect and Promote Public Health* [PowerPoint slides]. Presentation at the FDA PDUFA Public Meeting, Rockville, MD.

[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.

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 fiscal year 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 6 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).

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 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 thirty 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.

[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.

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 6 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-30s. 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 3 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 5 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 fiscal year 2009 through fiscal year 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

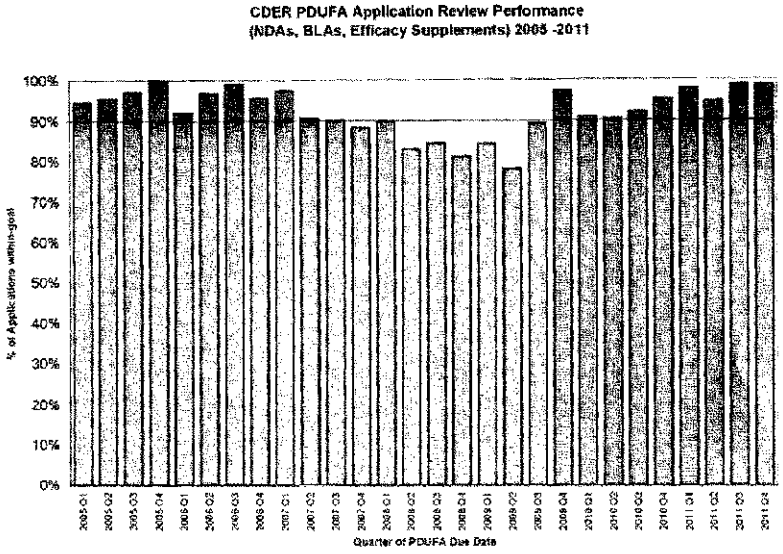
It should be noted that FDA assesses the benefit-risk of new drugs on a case-by-case basis, considering the degree of unmet medical need and the severity and morbidity of the condition the drug is intended to treat. This approach has been critical to increasing patient access to new drugs for cancer 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 decisionmaking.

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 fiscal year 2008–9, 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 2.



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 5 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. I will briefly summarize these enhancements.

A. Review Program for New Drug Applications, New Molecular Entities, and Original Biologics License Applications

FDA's existing review performance goals for priority and standard applications—6 and 10 months respectively—were established in 1997. Since that time, additional requirements in the drug review process have made those goals increasingly challenging to meet, particularly for more complex applications like new molecular entity (NME) NDAs and original BLAs. FDA also recognizes that increasing communication between the Agency and sponsors during the application review has the potential to increase efficiency in the review process.

To address the desire for increased communication and greater efficiency in the review process, we agreed to an enhancement to FDA's review program for NME NDAs and original BLAs in PDUFA–V. This program includes pre-submission meetings, mid-cycle communications, and late-cycle meetings between FDA and sponsors for these applications. To accommodate this increased interaction during regulatory review, as agreed to with industry, FDA's review clock would begin after the 60-day administrative filing review period for this subset of applications. The impact of these modifications on the efficiency of drug review for this subset of applications will be assessed during PDUFA–V.

B. Enhancing Regulatory Science and Expediting Drug Development

The following five enhancements focus on regulatory science and expediting drug development.

1. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

FDA recognizes that timely interactive communications with sponsors can help foster efficient and effective drug development. In some cases, a sponsor's questions may be complex enough to require a formal meeting with FDA, but in other instances, a question may be relatively straightforward such that a response can be provided more quickly. However, our review staff's workload and other competing public health priorities can make it challenging to develop an Agency response to matters outside of the formal meeting process.

This enhancement involves a dedicated drug development communication and training staff, focused on improving communications between FDA and sponsors during development. This staff will be responsible for identifying best practices for communications between the Agency and sponsors, training review staff, and disseminating best practices through published guidance.

2. Methods for Meta-analysis

A meta-analysis typically attempts to combine the data or findings from multiple completed studies to explore drug benefits and risks and, in some cases, uncover what might be a potential safety signal in a pre-market or post-market context. However, there is no consensus on best practices in conducting a meta-analysis. With the growing availability of clinical trial data, an increasing number of meta-analyses are being conducted based on varying sets of data and assumptions. If such studies conducted outside FDA find a potential safety signal, FDA will work to try to confirm—or correct—the information about a potential harm. To do this, FDA must work quickly to conduct its own meta-analyses to include publicly available data and the raw clinical trial data submitted by drug sponsors that would typically not be available to outside researchers. This is resource-intensive work and often exceeds the Agency's on-board scientific and computational capacity, causing delays in FDA findings that prolong public uncertainty.

PDUFA–V enhancements include the development of a dedicated staff to evaluate best practices and limitations in meta-analysis methods. Through a rigorous public comment process, FDA would develop guidance on best practices and the Agency's approach to meta-analysis in regulatory review and decisionmaking.

3. Biomarkers and Pharmacogenomics

Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time by helping to demonstrate benefits, establish unmet medical needs, and identify patients who are predisposed to adverse events. FDA provides regulatory advice on the use of biomarkers to facilitate the assessment of human safety in early phase clinical studies, to support claims of efficacy, and to establish the optimal dose selection for pivotal efficacy studies. This is an area of new science where the Agency has seen a marked increase in sponsor submissions to FDA. In the 2008–10 period, the Agency experienced a nearly fourfold increase in this type of review work.

PDUFA–V enhancements include augmenting the Agency's clinical, clinical pharmacology, and statistical capacity to adequately address submissions that propose to utilize biomarkers or pharmacogenomic markers. The Agency would also hold a public meeting to discuss potential strategies to facilitate scientific exchanges on biomarker issues between FDA and drug manufacturers.

4. Use of Patient-reported Outcomes

Assessments of study endpoints known as patient-reported outcomes (PROs) are increasingly an important part of successful drug development. PROs measure treatment benefit or risk in medical product clinical trials from the patients' point of view. They are critical in understanding drug benefits and harm from the patients' perspective. However, PROs require rigorous evaluation and statistical design and analysis to ensure reliability to support claims of clinical benefit. Early consultation between FDA and drug sponsors can ensure that endpoints are well-defined and reliable. However, the Agency does not have the capacity to meet the current demand from industry.

PDUFA–V enhancements include an initiative to improve FDA's clinical and statistical capacity to address submissions involving PROs and other endpoint assessment tools, including providing consultation during the early stages of drug development. In addition, FDA will convene a public meeting to discuss standards for PRO qualification, new theories in endpoint measurement, and the implications for multinational trials.

5. Development of Drugs for Rare Diseases

FDA's oversight of rare disease drug development is complex and resource intensive. Rare diseases are a highly diverse collection of disorders, their natural histories are often not well-described, only small population sizes are often available for study, and they do not usually have well-defined outcome measures. This makes the design, execution, and interpretation of clinical trials for rare diseases difficult and time consuming, requiring frequent interaction between FDA and drug spon-

sors. If recent trends in orphan designations are any indication, FDA can expect an increase in investigational activity and marketing applications for orphan products in the future.

Another PDUFA–V enhancement includes FDA facilitation of rare disease drug development by issuing relevant guidance, increasing the Agency's outreach efforts to the rare disease patient community, and providing specialized training in rare disease drug development for sponsors and FDA staff.

C. Enhancing Benefit-Risk Assessment

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 decisionmaking. Part of FDA's decisionmaking 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.

PDUFA–V enhancements include expanded implementation of FDA's benefit-risk framework in the drug review process, including holding public workshops to discuss the application of frameworks for considering benefits and risks that are most appropriate for the regulatory setting. FDA would also conduct a series of public meetings between its review divisions and the relevant patient advocacy communities to review the medical products available for specific indications or disease states that will be chosen through a public process.

D. Enhancement and Modernization of the FDA Drug Safety System

The enhancements for PDUFA–V include two post-market, safety-focused initiatives.

1. Standardizing Risk Evaluation and Mitigation Strategies

FDAAA gave FDA authority to require a Risk Evaluation and Mitigation Strategy (REMS) when FDA finds that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. Some REMS are more restrictive types of risk management programs that include elements to ensure safe use (ETASU). These programs can require such tools as prescriber training or certification, pharmacy training or certification, dispensing in certain health care settings, documentation of safe use conditions, required patient monitoring, or patient registries. ETASU REMS can be challenging to implement and evaluate, involving cooperation of all segments of the health care system. Our experience with REMS to date suggests that the development of multiple individual programs has the potential to create burdens on the health care system and, in some cases, could limit appropriate patient access to important therapies.

PDUFA–V enhancements initiate a public process to explore strategies and initiate projects to standardize REMS with the goal of reducing burden on practitioners, patients, and others in the health care setting. Additionally, FDA will conduct public workshops and develop guidance on methods for assessing the effectiveness of REMS and the impact on patient access and burden on the health care system.

2. Using the Sentinel Initiative to Evaluate Drug Safety Issues

FDA's Sentinel Initiative is a long-term program designed to build and implement a national electronic system for monitoring the safety of FDA-approved medical products. FDAAA required FDA to collaborate with Federal, academic, and private entities to develop methods to obtain access to disparate data sources and validated means to link and analyze safety data to monitor the safety of drugs after they reach the market, an activity also known as "active post-market drug safety surveillance." FDA will use user fee funds to conduct a series of activities to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action, e.g., labeling changes, post-marketing requirements, or post-marketing commitments. This may shorten the time it takes to better understand new or emerging drug safety issues. PDUFA–V enhancements will enable FDA to initiate a series of projects to establish the use of active post-market drug safety surveillance in evaluating post-market safety signals in population-based databases. By leveraging public and private health care data sources to quickly evaluate drug safety issues, this work may reduce the Agency's reliance on required post-marketing studies and clinical trials.

E. Required Electronic Submissions and Standardization of Electronic Application Data

The predictability of the FDA review process relies heavily on the quality of sponsor submissions. The Agency currently receives submissions of original applications and supplements in formats ranging from paper-only to electronic-only, as well as hybrids of the two media. The variability and unpredictability of submitted formats and clinical data layout present major obstacles to conducting a timely, efficient, and rigorous review within current PDUFA–goal timeframes. A lack of standardized data also limits FDA's ability to transition to more standardized approaches to benefit-risk assessment and impedes conduct of safety analyses that inform FDA decisions related to REMS and other post-marketing requirements. PDUFA–V enhancements include a phased-in requirement for standardized, fully electronic submissions during PDUFA–V for all marketing and investigational applications. Through partnership with open standards-development organizations, the Agency would also conduct a public process to develop standardized terminology for clinical and nonclinical data submitted in marketing and investigational applications.

F. User Fee Increase for PDUFA–V

The cost of the agreed upon PDUFA–V enhancements translates to an overall increase in fees of approximately 6 percent.

G. PDUFA–V Enhancements for a Modified Inflation Adjuster and Additional Evaluations of the Workload Adjuster

In calculating user fees for each new fiscal year, FDA adjusts the base revenue amount by inflation and workload as specified in the statute. PDUFA–V enhancements include a modification to the inflation adjuster to accurately account for changes in its costs related to payroll compensation and benefits as well as changes in non-payroll costs. In addition, FDA will continue evaluating the workload adjuster that was developed during the PDUFA–IV negotiations to ensure that it continues to adequately capture changes in FDA's workload.

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 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 Files[6] 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 facili-

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[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*.

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

ties. 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.

Overview of the Proposed Generic Drug User Fee Program

To develop recommendations for a generic drug user fee effective beginning fiscal year 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 API[8] 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.

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[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.

[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).

Development of biosimilars is expected to be less risky, less costly, and take less time; therefore, approved biosimilars are expected to be less expensive than the reference product. This program will provide significant benefits for patients, making available more affordable treatments that clinicians will know are biosimilar or interchangeable. The development of this new market segment will expand the opportunities for technical innovation and job growth.

Background

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

Under the transition provisions in the BPCI Act, user fees for a biosimilar biological product are assessed under PDUFA. Accordingly, currently, user fees for biological products are the same, regardless of whether the 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 fiscal year 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.

CONCLUSION

PDUFA–IV expires 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 accomplishments, it is critical that the reauthorization occur seamlessly without any gap between the expiration of the old law and the enact-

ment of PDUFA–V. The passage of both a new generic drug user fee and a new biosimilars user fee would allow FDA to build upon the success of PDUFA.

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

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

Dr. Shuren.

STATEMENT OF JEFFREY SHUREN, M.D., J.D., DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. SHUREN. Mr. Chairman and members of the committee, I am Dr. Jeff Shuren, Director of Center for Devices and Radiological Health, or CDRH, at the FDA. Thank you for the opportunity to testify today.

I am pleased to tell you that 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 16.

These recommendations would authorize FDA to collect $595 million in user fees over 5 years to help fund a portion of the agency's medical device review program with FDA agreeing to certain overall performance goals. As required by law, we held a public meeting yesterday and will receive public comments on the proposal package until April 16 before sending a final package to Congress in late April.

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 have not done as good a job managing the review programs as we should have.

The No. 1 problem we found was insufficient predictability, which was leading to inefficiencies, higher costs for industry and FDA, and 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, 27 actions have been completed or are well underway. They are intended to create a culture change toward greater transparency, interaction and appropriate balancing of benefit and risk. They focus on assuring predictable and consistent decisionmaking, and application of the least burdensome principle, and implementing more efficient regulatory processes.

We believe that these actions have had, and will have, a visible, positive impact by providing greater predictability about data requirements through guidance, reducing unnecessary or inconsistent data requests through training, and policy and process changes, implementing policies that lead to appropriately balanced benefit-risk determinations, using external experts more extensively and effectively, creating incentives to conduct clinical studies first in the United States, speeding up clinical trial approval decisions, and implementing the innovation pathway.

Preliminary data indicates 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 is continuing to decline in 2012. 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 will also include 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 work on the submission, ensuring that no submission is left behind. Requiring a new, substantive interaction between FDA and an applicant halfway through the targeted time for reviewing the application, would help assure sufficient time for the applicant to properly respond to appropriate questions. Clear criteria for when FDA will refuse to accept an incomplete application means more efficient use of resources to the benefit of both FDA and industry.

These and other proposed enhancements are intended to achieve a shared outcome goal of reduced average total time to the 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 are concerned 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.

When PDUFA was last reauthorized in 2007, as Mr. Enzi, you pointed out, 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 MDUFA program goals and achieving timely access to safe and effective devices, which is an objective that we share with industry, healthcare professionals, patients, consumers, and you.

Mr. Chairman, we share your goal of timely reauthorization of MDUFA, and I look forward to working with you toward enactment of this critical legislation.

I commend the committee's efforts, and am pleased to answer any questions the committee may have.

[The prepared statement of Dr. Shuren follows:]

PREPARED STATEMENT OF JEFFREY SHUREN, M.D., J.D.

INTRODUCTION

Mr. Chairman and members of the committee, 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 fiscal year 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 fiscal year 2010—currently account for about two-thirds of the drug review program's budget, and the current fee for fiscal year 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 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

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[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*.

[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*.

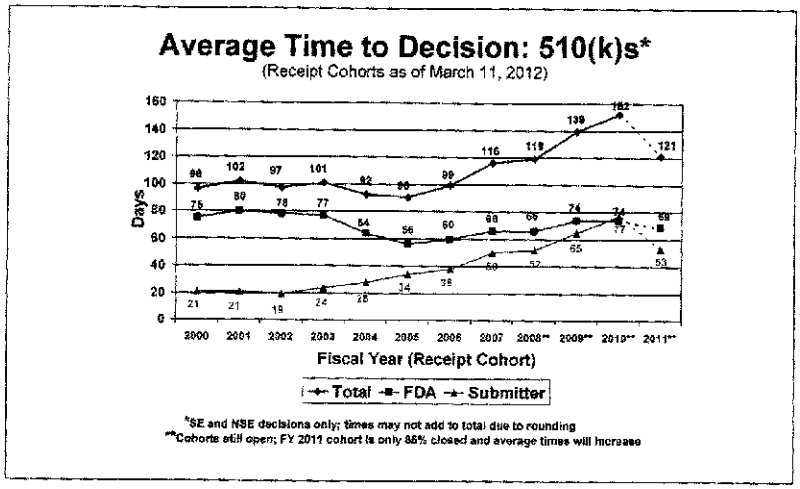
System, an implantable electronic device that stimulates the diaphragm and allows certain spinal cord injury patients to breathe for at least 4 hours a day without a mechanical ventilator.[5]

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

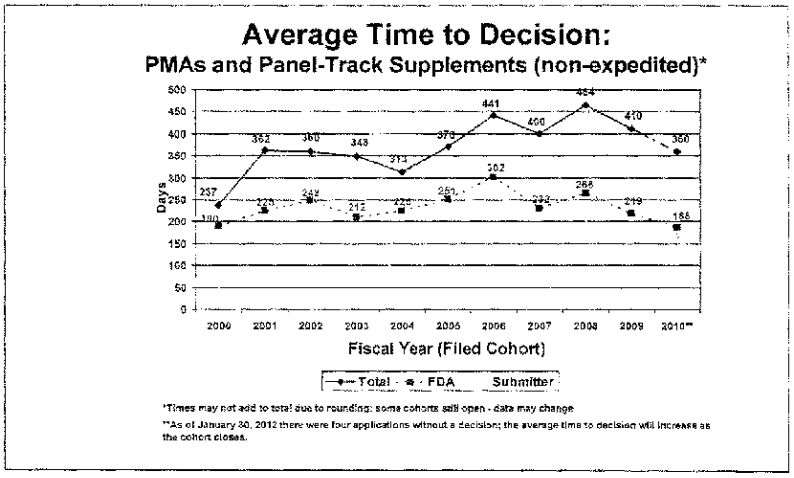
FDA has been meeting or exceeding goals agreed to by FDA and industry under MDUFA II for approximately 95 percent of the submissions we review each year. For example, FDA completes at least 90 percent of 510(k) reviews within 90 days or less. In the few areas where FDA is not yet meeting its MDUFA goals,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

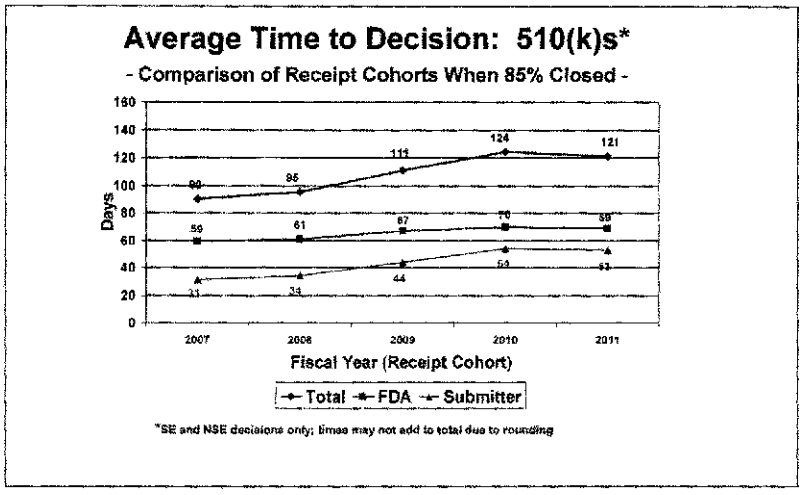


[5] See FDA News Release, "FDA Approves Diaphragm-Pacing Device" (June 18, 2008), available at *http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm116914.htm*.

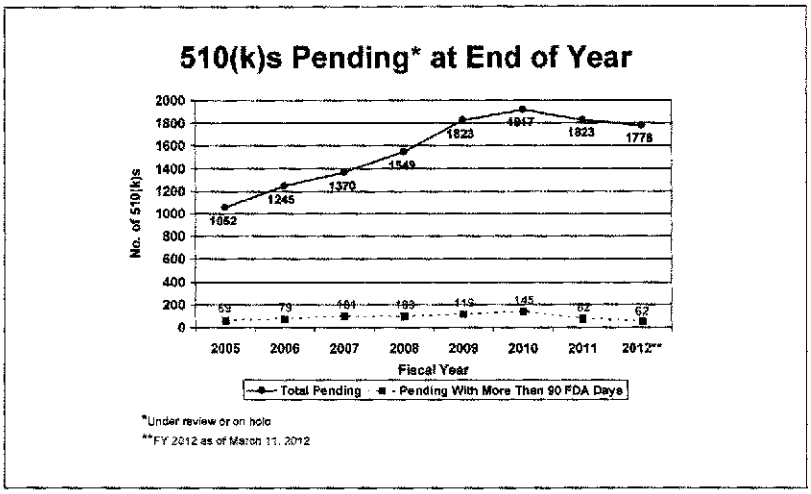
[6] Guidance documents include documents that relate to: (1) the design, production, labeling, promotion, manufacturing, and testing of regulated products; (2) the processing, content, and evaluation or approval of submissions; and (3) FDA's inspection and enforcement policies. See generally, "Food and 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*.



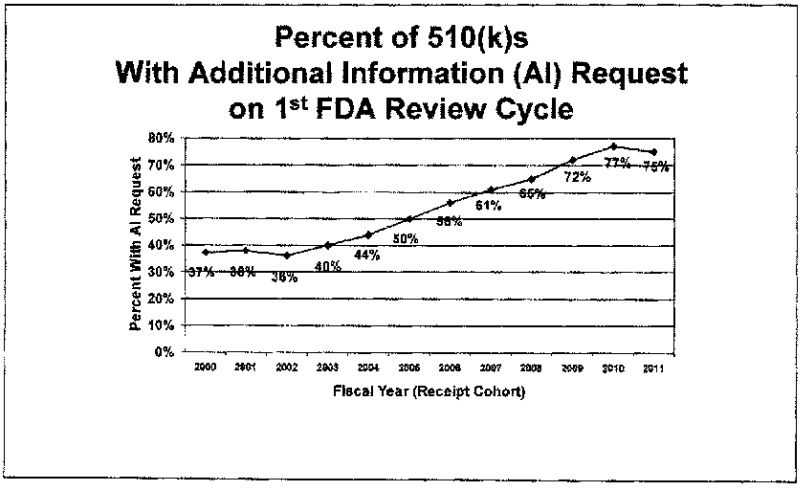
FDA bears some responsibility for the increase in total time to decision, and we have been instituting management, policy, and process changes to address this issue. As a result, we are starting to see indicators of improved review performance. For example, the Agency has currently completed review of 85 percent of the 510(k) submissions received in fiscal year 2011. The graph below, illustrating average time to decision during the last 5 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 fiscal year 2011, CDRH for the first time began reducing what previously was an increasing backlog of unresolved 510(k) submissions, as indicated in the next chart—and that trend is clearly continuing as we approach the mid-point of fiscal year 2012.



Likewise, there had been a continuous annual increase, since fiscal year 2002, in the percentage of 510(k) submissions requiring an Additional Information (AI) letter [7] 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 fiscal year 2011, the percentage of 510(k)s requiring an AI letter declined for the first time since 2002.



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

[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.

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 2 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 decisionmaking, 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 No. 1 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 dialog 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 March 2012, 27 actions are already completed or 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, in-

[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 Web site at *http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm276 286.htm*.

cluding the creation of a new approach for important, new technologies called the Innovation Pathway.

Since then, we have announced additional efforts to improve our premarket programs, including actions to improve our program for clinical trials and the Investigational Device Exemption (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, decisionmaking, 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 decisionmaking (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 April 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 timeframes associated with each strategy and specific actions we will take to meet those goals or make significant progress toward achieving those goals, including, for example:

- By April 1, 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, implementing the Innovation Pathway 2.0 (a priority review program to expedite development, assessment, and review of important technologies), 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) rate[12] 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 next chart, from a peak of 8 percent in fiscal year 2010, the NSE rate has decreased to 4 percent by the end of the first 5 months of fiscal year 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 5 months of fiscal year 2012, as shown in the chart below.

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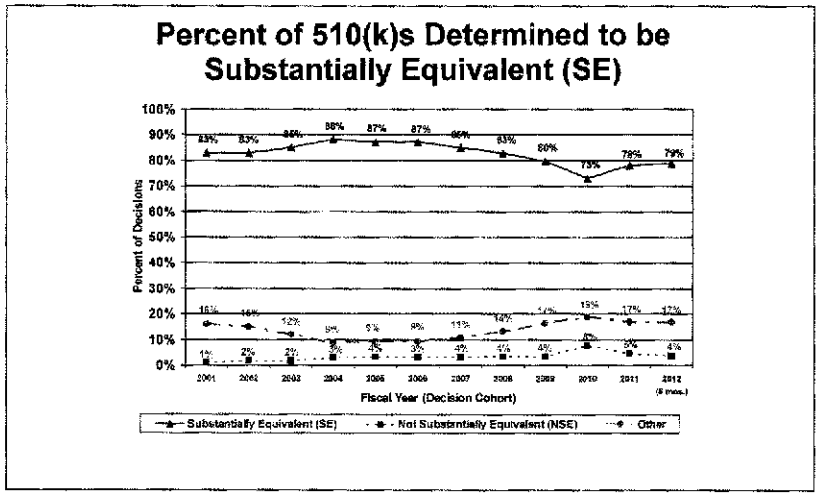
[10] CDRH, "2012 Strategic Priorities," available at *http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/ucm288735.htm*.

[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 Web site at *http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm199906.htm*.

[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 meeting [13] 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 last month that 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 5 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 recommend-

[13] A transcript of the September 2010 public meeting, and related meeting materials, are available on FDA's Web site 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 Web site 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 Web site at *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm236902.htm*.

ations,[16] requested written public comment on those proposed recommendations, and announced that we would be holding a public meeting on March 28, 2012, at which interested stakeholders could present their views.

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 fiscal year 2015;
    - increasing the percentage of PMA reviews that are completed within 180 review days, from the current 60 percent to 90 percent by fiscal year 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 fiscal year 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.

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[16] The proposed package of recommendations for MDUFA III is available on FDA's Web site at *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm292860.htm*.

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 Web site 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. After the conclusion of the public comment period on April 16, 2012, FDA will consider the public's views and comments, 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]

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 require premarket data that demonstrate 'clinical efficacy,'" and "[t]he device industry should

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[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*.

[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_1rev_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*.

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.

Most recently, France's Directorate General for Health and its consumer safety body AFSSAPS[23] issued a report[24] 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 pre-eminence in medical technology innovation, and we support the current regulatory framework in the United States."[26]

CONCLUSION

Over the course of MDUFA II, and especially during the last 2 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, decisionmaking, 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,

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[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. 1115–30 (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," *BMJOpen* (May 2011), available at *http://bmjopen.bmj.com/content/early/2011/05/12/bmjopen–2011–000155.full.pdf*.

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

[24] See AFSSAPS, "Poly Implant Prothesè: 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).

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 committee, 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.

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

We will begin a round of 5 minute questions. We have a good turnout here today, so we will try to move right along.

Starting with you, Dr. Shuren, we hear a lot about speeding up the review times for devices, applications.

Referring back to your testimony, which I had gone over last evening, you said, "Our goal is not more regulation or less regulation, but smart regulation." You said, "Our goal has been to ensure that safety and effectiveness and innovation are complementary,"—complementary—"mutually supporting aspects of our mission to promote the public health."

We hear a lot about speeding up review times, but how will user fees be used to ensure that devices are safe for patients? Safe.

Dr. SHUREN. What is critical in the user fee agreement along those lines is we are not changing the standards for a product to come to market.

These fees are going to allow us to put in place process improvements, and have the staff to make well-informed and timely decisions assuring that those products are safe and effective when they are coming to market. We will not shortchange the quality of our decisions. What we will do is be able to speed up those decisions, but still assure the safety and effectiveness of devices coming forward.

The CHAIRMAN. The same question I will ask of Dr. Woodcock is how would patients be affected if we did not reauthorize this on time? How would your patients be affected, both of you, Dr. Shuren, on your devices and then Dr. Woodcock?

Dr. Shuren.

Dr. SHUREN. We would have to let go staff and it is more than just that. Our program will actually be in a death spiral because our good people will leave the program, it will go down. There will be delays in reviewing products. There will be disincentives for innovation and that will lead to new technologies, jobs, all going overseas. That is not in the best interest of patients. It is not in the best interest of industry. It is not in the best interests of the U.S. Government.

The CHAIRMAN. Thank you. Dr. Woodcock. How would patients be affected if we did not get the prescription drug user fees?

Dr. WOODCOCK. The Prescription Drug User Fee Act, if terminated, would require us to begin to layoff a large number of staff involved in review, and also probably some involved in managing drug safety post-marketing.

We would go back to the point, unfortunately, where innovative products are reaching American patients last in the world instead of first in the world.

But in addition, the other user fee programs also provide, for example, the generics. We need a robust generic drug industry because 80 percent of prescriptions dispensed in this country are generic drugs, and our patients rely upon those drugs: their safety, their quality, and their affordability. So that program needs more support to keep building on its success.

The CHAIRMAN. Dr. Woodcock, let me followup with another question. I have heard from many members of the rare disease community about the unique challenges that this community faces in getting drugs developed and approved to treat their serious ailments.

How does PDUFA–V, as we are calling it, enhance focus on orphan drugs for rare diseases?

Dr. WOODCOCK. The program includes enhancements of our ability to support those companies that are developing a rare disease—their specific support added will be able to add staff because often, these are small companies that need a great deal of advice.

There is also a provision for assisting small companies where we will be adding significant staff that will be able to help small companies or new companies through the review and approval process.

The CHAIRMAN. Very good. That is all I have for right now unless I have another second round.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

I will begin with Dr. Shuren. The proposed medical device user fee agreement will give you resources to hire and train more reviewers, more managers, and more technical writers.

What effect can we expect and how will you make that happen? What kind of training?

Dr. SHUREN. We have already put in place a new reviewer certification program. Every new reviewer that comes in the door, now goes through standardized coursework, oversight of the applications that they are reviewing.

We are going to follow that up this year, and actually in the next few weeks, with a pilot for what we call an experiential learning program. We are going to let our staff go out to manufacturer facilities, healthcare facilities, and get real world experience.

We are also putting in place core curriculums for each of the critical roles in our center in premarket review and elsewhere. This includes for managers, medical officers, lead reviewers, engineers, and on down the line.

Senator ENZI. Thank you.

Dr. Woodcock, the proposed prescription drug user fee agreement addresses issues concerning the Risk, Evaluation, and Mitigation Strategies, or REMS. REMS was intended as a tool to let the FDA

ensure that the benefits of a drug or biological product outweigh its risks, but implementation resulted in some delays and confusion.

Can you describe the challenges of implementing REMS over the past few years and how this agreement addresses the outstanding concerns?

Dr. WOODCOCK. Certainly. We think the REMS are a good tool because some drugs have to have additional safety measures to be on the market because they have some severe safety risk.

However, the original implementation of the REMS was not standardized, and it was one off for each REMS that was implemented. This caused difficulties for the manufacturers, but it also caused tremendous difficulties for the health care system.

We had a public meeting about this, and we heard, believe me, very clearly that we need standardized tools. We need one way to do this. It has to be convenient, both for the physicians, healthcare professionals, and the pharmacists in particular who have to implement these REMS. And the user fee program will provide us with the goals and the resources to do that.

Senator ENZI. Thank you.

This question will be for both of you because I see that the proposed, both fees, have provisions concerning the patient perspective on benefit-risk decisions.

What does that mean to each of you? Let's start with Dr. Woodcock.

Dr. WOODCOCK. We are very excited about these provisions because taken as a whole, we think they will move toward patient-centered drug development because, actually I hate to tell you, but drugs are not really safe. Most drugs have liabilities. They have risks, and so the benefits are taken into account with those risks.

But we need to understand what tradeoffs a patient is willing to take. What risks might they be willing to receive in order to get the benefits? And that tradeoff, we need to hear from patients. It turns out that doctors, or regulators, we do not really know, we do not really speak with a patient's voice.

The agreement proposes that we get 20 diseases, that we go through a process to elicit the patient's point of view, and we are piloting that now in obesity, and we are learning a great deal, even with this pilot we are doing.

We also are developing a standardized benefit-risk framework, which we would publish for each drug, that would go over the benefits, the risks, the uncertainties, and the alternative therapy, and let people know how the new therapy stacks up.

Then we hope to incorporate patient-reported outcomes into the trials, so we hear from the patient point-of-view how they experienced the disease and the drug, and how the drug mitigated the disease, as well as how the side effects burdened the patient.

This would really revolutionize, I think, our understanding when taken together of how therapies actually impact patients.

Senator ENZI. I will probably have a couple of followup questions, but I will go to Dr. Shuren first.

Dr. SHUREN. I share Dr. Woodcock's perspective, as does my center, how important it is to take into account what a patient perceives as a risk and what they are willing to take. As I tell my re-

viewers, they are not the ones who are getting these devices; the patients are and the patients have to make a choice.

We, too, under MDUFA–III have committed to develop a benefit-risk determination framework that takes into account patient's tolerance for risk. I am pleased to say that, actually, it was something we were pursuing. We put out a draft proposal in August of this year and we just issued the final framework on the 27th, this week. It will go into effect starting on May 1st. We are going to begin to do training of our staff, and it will move forward.

We, too, have committed for engagements with the patient community to better understand their perspective. We already have developed a survey tool that we are going to be piloting. We are also looking in the obesity context. We will be leveraging the meetings that CDHR is putting together and we think, together, this will actually move the program in a very positive direction.

Senator ENZI. Encouraging. My time has expired. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Enzi. I remind members of the committee that we have another panel of five after this panel. Also, it looks like we are going to have a vote here sometime soon, so we will have to take a break, so I ask all Senators to please respect the 5 minute time.

I have in order now, Senator Murray, Senator Roberts, Senator Mikulski, Senator Burr, and then Senators Whitehouse, Bennett, Murphy, Hagan, and Blumenthal.

Senator Murray.

STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman.

I really want to thank all of our witnesses for being here to talk about this really important issue. The medical device, pharmaceutical, and biotechnology industry is really working hard to find cures for diseases that affect millions of Americans and their families. Companies in this industry are also really critical to our local economies.

In my home State of Washington, biotech companies employ about 18,000 workers directly and almost 50,000 more through their economic activity. Medical device companies employ about 9,000 people and supports the employment of another 20,000.

These are not just any jobs. These are high-skilled, stable jobs that pay good wages. I think they are exactly the kind of 21st century careers we are all working hard to create here in America.

I am very encouraged by the success and growth of this industry, and that is why I am very focused, Mr. Chairman, on making sure the Federal Government is doing what it can to make sure they are successful, and why this important discussion is happening today. I am really pleased that we are working together to strengthen the FDA user fee system.

Dr. Woodcock, Dr. Shuren, you have answered my questions, and I know we have another panel. I just wanted to mention, Dr. Woodcock, you said, "If we do not reauthorize this, we will go from first to last," which is frightening, I think, for a lot of patients in this country, who really depend on the FDA. I really appreciate you pointing that out.

Dr. Shuren, I wanted to quickly ask you, can you give us an idea of some of the products or disease categories where FDA is currently leading the world in advancing innovation that would be impacted should we not reauthorize the user fees legislation?

Dr. SHUREN. I think you can actually go down the list of any innovative technology we want to get to patients here in the United States first.

If the program goes down, that will not even be a dream. It will be an impossibility.

Senator MURRAY. Thank you very much.

I do know you have another panel, Mr. Chairman, so I will wait to hear their testimony. Thank you.

The CHAIRMAN. Thank you, Senator Murray.

Senator Roberts.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Thank you, Mr. Chairman, for a very timely hearing. Thank you for your leadership.

And to all of the five witnesses, we always have obligations, and I apologize for not being here. But you have really put together an excellent panel following this panel.

I particularly want to thank Sara Radcliffe, who is speaking for BIO and its 1,100 members. She says in her testimony, "Given the recent establishment of the biosimilars at the FDA, only modest appropriations are currently allocated to the program." So, of course, they have agreed to, "An equitable balance of fees and appropriations," and that is what we are facing here in terms of user fees.

I do not like user fees, but under the circumstances, there is not any real alternative, and it is a challenge we face, I think, in almost every program that we have here before the Senate, regardless of what committee it is. But she sort of hit the nail on the head and I thank her for her testimony.

Then I would like to move, still on the second panel, a farmer points out that, "America in 2009. We are talking about 674,192 direct jobs, $918 billion for the total economic sector." So that is why this reauthorization is such an important factor, and this agreement holds.

I would also like to thank Dr. David Gaugh, I hope I am pronouncing that right, I apologize if I am not. But he says, and he is here to represent the generics,

> "By designing the programs to spread fees across multiple stakeholders and sources to keep individual amounts as low as possible, the programs will help assure that American consumers continue to receive a significant cost savings from generics,"

ET cetera, etc. My question is, how do we do that?

After all of that, I would like to ask our two witnesses, in terms of user fees, who really pays? Who really pays?

Dr. SHUREN. In reality, it is probably the American public who pays. They pay through——

Senator ROBERTS. Exactly, that is right.

Dr. SHUREN [continuing]. Appropriations and then the cost for user fees.

Senator ROBERTS. Yes, I know the appropriations.

Dr. SHUREN. Right.

Senator ROBERTS. And I know that we would like to have more appropriations, so would the Chairman, so would the Ranking Member, but it is going to be the public that pays the user fees. Now, with all of that, I do not need to ask you, Doctor, the exact same thing.

Dr. Woodcock, how exactly does the FDA plan to meet the commitments outlined in the agreements? How do we plan to meet these deadlines because, as you know, FDA has missed time and time again?

Dr. WOODCOCK. FDA is currently exceeding the vast majority of its PDUFA goals, and over the 20-year history of the program, we have met those goals consistently, except for immediately after the FDA Amendments Act, where we had the REMS and multiple other assignments.

Senator ROBERTS. Right.

Dr. WOODCOCK. We have crafted this very carefully to make sure that the goals will work for industry, but that are also achievable by us. And I have every confidence that we will meet the goals of the drug user fee programs that are proposed.

Senator ROBERTS. Good. And I hope the committee stands behind you in your endeavors, I am sure.

Now, I am concerned by comments I have heard recently that the culture at the FDA has changed and folks feel that FDA is moving away from working in a collaborative way with industry to more of a regulatory enforcement kind of culture.

Is that the case? Are we going to tell this committee about any improvements that are being made to the culture at FDA?

Dr. WOODCOCK. CDHR went through an entire culture effort over the last 4 years. And I think that we are not changing our approach to our standards of drug regulation.

The issues I have heard are that we are not able to interact with the industry as often as the industry would like, and we are not as transparent. I have looked into this, and it really is a workload issue.

In fact, the user fee, the prescription drug user fee program proposal that is before you explicitly addresses this issue.

Senator ROBERTS. OK.

Dr. WOODCOCK. And it puts a negotiation discussion——

Senator ROBERTS. OK. I am out of time and the Chairman is going to bang the gavel. So you are telling, basically us, if we do our job and get this done, you can do your job, and then industry will not complain about this issue.

I have one other question for Dr. Shuren, but I am out of time. I will just submit that for the record. Thank you for coming by my office, sir, and paying me a courtesy call. We had a good visit.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Roberts.

Senator Mikulski.

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Mr. Chairman, thank you for organizing this hearing as we are on the brink of an actual mark up of a variety of user fees. I am going to welcome our panel.

Mr. Chairman and colleagues, Maryland is the home of life science jobs. We are very proud of our innovation corridor and a substantial number of the jobs in that corridor are in research. NIH is an international icon and Hopkins speaks for itself.

But after the research, you have to deal with the valley of death, which is taking all the great research and converting it into products that people can use to have a better life and a sustained life. This is why I am excited about moving the user fees process forward.

I am proud of the 5,000 people who work at FDA at all levels. I am often dismayed about the harassment and hazing that these employees go through from the public—cheap political shots and cutesy one-liners at town hall meetings. Despite this harassment, we expect them to show up every day with an attitude of, "Hoo-rah, hoo-rah!" and be ready to work with us. So I think we need to get real, as we have very real expectations of them.

Now let me move on to my questions.

In regard to this whole user fee process, I have been involved in every user fee since 1992. I thought this version had intellectual rigor and had a process that was open and transparent. That process actually engages with industries in conversation and, even taken corrective action with the certification program. This authorization is welcoming everyone to the table.

Having said that, however unlike other authorizations, we have sunsets on the user fees. If we do not act in light of these sunsets, what would be the consequences to the workforce in FDA?

Dr. SHUREN. We would lose all the positions being supported by user fees and more because——

Senator MIKULSKI. Because you would have to give RIF notices?

Dr. SHUREN. We would have to give RIF notices.

Senator MIKULSKI. When would you have to give RIF notices?

Dr. SHUREN. As a matter of regulations, it would start around July, about that time. We are required to give at least 60 days advance notice, and then start to wind down the program.

Senator MIKULSKI. Approximately how many employees would that involve?

Dr. SHUREN. It would involve approximately 250. The problem is once people know that is happening, more people leave, and that is a problem.

Senator MIKULSKI. So I say, Mr. Chairman and colleagues, if we are talking about RIF notices in July, we know that people will begin to worry in May and April. We need to really adhere to your mark up schedule in a very rigorous way. A mark up in April would keep the process and morale going as we work out our legislative issues.

Am I correct in thinking that?

Dr. SHUREN. Yes.

Senator MIKULSKI. In summary, we should have a sense of urgency and adherence to our own timelines and compliance issues?

Dr. SHUREN. I have to tell you that message alone would be very welcome by the staff at FDA. They are really looking for help, and knowing the commitment of this committee, and the process is moving quickly and help is on the way, and this program will survive, and will mean a lot. And it will help us move things forward.

Senator MIKULSKI. That is heartening to hear, and I think we need to take it to heart.

Now, lets talk about all the bipartisan agreements and letters of agreement with the industries. I am sure both of you, have participated in and read these agreements. Do you feel that the agreements offer guidance? Further, do you feel satisfied with the three drug agreements in existence, and also the two new agreements in generic and biosimilar? I know these agreements contain pretty sophisticated science and complicated regulatory measures, but do you feel if we follow any of those five agreements you have flashing yellow lights?

Dr. WOODCOCK. For the drug agreements, we feel very confident about all three of them that they will accomplish our mutual goals of getting these products through in a timely and sound way, and also supporting the safety of products for the United States.

Senator MIKULSKI. What about biosimilar and generic?

Dr. WOODCOCK. The same. The generics are, as you know, directed partly at improving and assuring the quality and safety of the generics no matter where they are sourced in the world. We regard this as a critical issue.

Senator MIKULSKI. Oh, I know. We could talk about that issue as a whole separate hearing.

Dr. WOODCOCK. And the biosimilars, we are very confident that we can enact a biosimilars program and we are doing that now. However, as these applications really start to roll in, we will need the staff to support this program. We will need additional resources.

Senator MIKULSKI. And the training.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Mikulski.

Senator Burr.

STATEMENT OF SENATOR BURR

Senator BURR. Mr. Chairman and my colleagues, the proposed reauthorization is an unprecedented level of user fees. There is going to be on our part the need for an unprecedented level of oversight, transparency, and accountability as part of these reauthorizations, and I hope my colleagues will remember that.

Dr. Coburn and I are releasing a GAO report today that confirms a disturbing trend: the FDA is taking longer and longer to make final decisions on life-saving medical devices. GAO also confirms that the FDA is not meeting some of its performance goals.

I would like to take this opportunity today to share some of the key findings of this report with my colleagues because I think it is crucial and critical that we consider these findings as we work through the user fee reauthorizations.

Let us start with the findings that relate to PMA's, and I quote their GAO report,

"The FDA was inconsistent in meeting performance goals for PMA submissions. The average time to final decision for original PMA's increased from 462 days for fiscal year 2003 to 627 days for fiscal year 2008, which is the most recent year for which complete data was available."

I go on to quote,

"This report shows that the average number of review cycles increased for certain PMA's, while the percentage of PMA's approved after one review cycle generally decreased."

Now, let us look at the 510(k)'s, and I quote,

"Even though FDA met all medical device performance goals for 510(k)'s, the elapsed time from submission to final decision has increased substantially in recent years from fiscal year 2005 through fiscal year 2010, the average time to final decision for 510(k)'s increased 61 percent."

It goes on to quote,

"The average number of review cycles in FDA's request for additional information for 510(k) submissions also increased.

"Clearly, reporting only on the user fee performance goals negotiated by the industry and the FDA does not paint a full picture of the FDA's performance and how well the agency is fulfilling its public health mission. The proposed user fee agreements have been sent to Congress for reauthorization. The goal of the user fees is to ensure timely review and action on medical products.

"This is why increasing times are so concerning. Patients rely upon FDA to make sound medical decisions in as timely a manner as possible. Increasing regulatory uncertainty and unnecessary delays are stifling investment in the development of lifesaving medical devices.

"If Congress fails to ensure consistent oversight and transparency at the FDA, we risk continuing to drive medical innovation and job creation overseas, jeopardizing American patients' access to the most cost-cutting medical devices created."

So where do we go from here? I know you are probably going to tell us a little more about all the new initiatives that the FDA has committed to put in place, and there are some good concepts. I commend you for some of the changes that you have made within CDRH.

Comments were made 5 years ago and they have not been met. A doubling of user fees is not going to guarantee the agency meets its goal. If we are going to fix what is not working that well at the FDA, these commitments have to be fulfilled consistent with the law.

My question to you, Dr. Shuren, is at the end of the day, what are the clear matrix by which CDRH will be held to ensure that the qualitative and quantitative goals agreed to under this proposed agreement are fulfilled? In other words, what are the metrics Congress and the American people can use to measure if the commitments made in this agreement and the steps FDA is proactively taking to address concerns are actually translating into more predictable and consistent day-to-day action across CDRH?

Dr. SHUREN. In our commitment letter, we have two pages of metrics that we are committing to. In fact, the largest section in the commitment letter goes to our reporting on metrics and transparency.

In MDUFA–II, we have reported over the 5 years on about 157,000 data points in our quarterly reports and 180,000 data points in our annual reports. In MDUFA–III, it will be 10 times the amount. By the end of the 5 years, we will have reported on over 3 million data points. That is more than you will see for any other country.

We are being very transparent in what we do, and we are putting in tough metrics. I will say what we are putting in this time is a metric for total time. This is a shared goal. It requires work on our part. It requires work on industry's part and that is reflected in the commitment letter.

I will note in the GAO report, that they also talk about the actions we are taking to address the challenges facing the program. They, too, have acknowledged that the actions we are taking are directed, and it looks like they will address those challenges. I am very glad to see that reflected in the report as well.

Senator BURR. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Burr.

Senator Whitehouse.

STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Thank you, Chairman.

Kenny Sparks from Little Compton, RI was diagnosed 6 years ago with a disease called frontotemporal dementia. He died last year on August 30, 2011 and his wife Cheryl said that it was a, "Difficult and lonely journey."

One of the reasons it was a difficult and lonely journey was because this was a rare disease and there were few treatments and no cure. So I would urge you to continue to press forward in every way you can to make sure that the orphan drugs, as the Chairman mentioned, are pursued so that that journey for these families becomes a little less lonely.

My question to you, however, is about foreign manufacture of pharmaceuticals. Things have changed in this industry. What used to be very much a home built industry is now reliant on international supply chains. We do not inspect international factories.

How much has this problem grown recently? How urgent is this problem? And do you think the steps we have taken to address it are adequate?

Dr. WOODCOCK. There are two issues here. One is FDA's ability to inspect those foreign facilities, and the generic drug user fee program squarely addresses that, and will level the playing field, and make sure that the intensity of inspection, domestic, foreign, no matter where, will be the same. We will be able to use a risk-based approach to inspection.

The other issue, though, is the tools that we might have to keep counterfeit or improperly manufactured drugs out of the U.S. drug supply. There, of course, we do not have modern tools, probably because the statute was written at a time when domestic manufacture was really the norm and was considered.

For example, we really do not have the ability based on our suspicions to stop drugs at the border if we have suspicion. We have a burden of proof that we have to prove something is wrong, and I find that shocking, and I think that American consumers would find that shocking as well.

There are additional tools, I think, that other countries certainly have to stop products at their border that are suspicious and other enforcement tools that we currently lack.

Senator WHITEHOUSE. Thank you very much.

Do you care to add anything else, Doctor? Do you care to add anything?

Dr. SHUREN. Regarding shortages, we had to deal with a slightly——

Senator WHITEHOUSE. No. The question was regarding the international supply chain and its integrity, and what that means for American consumers.

Dr. SHUREN. Yes, I was just going on the shortage side with the supply chain for devices, but we do have concerns about assuring the integrity of the supply chain.

On the device side, we deal with certain different kinds of challenges, but we also have issues with foreign sourcing. Many of the companies do just-in-time production, and because devices are becoming increasingly complex, as they rely on foreign suppliers, just a problem with one component in a device can hold up the manufacturing and the availability of that technology even when all the different parts and components may be available.

Senator WHITEHOUSE. Thank you, Chairman.

The CHAIRMAN. Thank you, Senator Whitehouse.

Senator Isakson.

STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Mr. Chairman, I will defer. I just walked in the room, and I would probably be repetitive. So I will defer to the next questioner.

The CHAIRMAN. Thank you, Senator Isakson.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman.

I want to start by saying how grateful I am and Colorado is for your leadership here.

The CHAIRMAN. Thanks.

Senator BENNET. And for the Ranking Member's leadership in producing this bipartisan basis for this legislation going forward.

It is not only important for all the reasons Senator Mikulski said and the urgency of getting this done, I think it sets a model for what the rest of Congress should be doing. I am very proud to have the chance to work with both of you on this, and with my democratic and republican colleagues on a series of important bills here.

I wanted to ask Dr. Woodcock, in that context, about drug innovation. This area of drug and biotech innovation is of great interest to me because Colorado has a growing bioscience community with

cutting edge researchers. They are desperate that this not move overseas, and I know the FDA does not want that either.

In an effort to work across the aisle, Senators Hatch, Burr, and I have introduced a bill that would provide certainty when drugs show promising prospects or even dramatic results early on. And I know you have been a strong advocate of having a more formal designation for breakthrough therapies.

Can you talk to us about how you see this working at FDA, and give us some examples of products where this would be a helpful designation, where today there is none?

Dr. WOODCOCK. Certainly, and I thank you for your leadership and the other members for their leadership on this issue.

Today, with modern science, we are seeing something that we rarely saw before with therapeutics, which is sometimes very early in human testing. Sometimes it is the very first low doses that are carefully given to people, we see responses to the treatment that we have never seen before. And this might be for a serious and life threatening disease such as a dementia, where no treatment exists, it is effective.

When that happens, we need what I call, "all hands on deck." Everybody needs to sit up straight, get together, and figure out how to evaluate that therapy as rapidly as possible, so that if it actually has the promise that it shows in that early testing, it can be moved to patients as quickly as possible.

Some of these may fail. However, the fact that some of them may work and actually be a breakthrough for patient and offer treatment that has never been seen before, a benefit, means that we have an ethical obligation to work as rapidly as possible.

The designation process, I believe, would get everyone's attention. There would be an obligation to get that development path as efficient as possible. We also can run into ethical problems.

If you had a serious or life threatening disease, and there was a tremendously promising therapy, would you want to be on the placebo group for 6 months?

We need to design trials and evaluations that also take those issues into account. As soon as we lose what is called "clinical equipoise," and as soon as we think the therapy is much more likely to be better than anything out there, we need to take the appropriate steps.

That is what this is about. It is different than Fast Track, which is actually a designation about review and working, rolling review and working with the company, and so forth. This is for those exceptional therapies which, we hope with the new science, we are going to be seeing more often where we really have to pay attention.

Senator BENNET. I think it is a critical component of trying to create a patient-centric approach here. So I appreciate very much your words.

Dr. Shuren, I do not have a lot of time left, and you and I have gone over some of this before, and you have been kind enough to visit Colorado, which I deeply appreciate.

I wonder if you could talk specifically about how the user fees, in your view, are going to help smaller and mid-size companies

that may not have the same resources as larger ones navigate the FDA?

Dr. SHUREN. There are a number of improvements and enhancements that we will see under MDUFA–III, and I will just highlight a few.

One of them is in the pre-submission process. That is where now a company can come to us before they have actually even done the testing, or a lot of testing on their product, to get advice from us. This will be a much more rigorous process where we provide that advice. We write it down. We stand behind it, unless we wind up generally getting new information that is raising new issues. That is a big deal for these companies to have that kind of advice.

The second is we are getting some additional people. It is only five. But you know what? Five can help a lot for putting out more guidance documents. We think putting out guidance is critical. It provides clarity, transparency, and predictability for companies. And this will help us get there.

I will make one comment on that, though. On the drug side, a much bigger program, they have about 82 people in their office who handles those regulatory issues, guidance in those rules. We are at 18; the 5 will put us up to 23. It will help, but we have a way to go.

Senator BENNET. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Bennet.

Senator Merkley

STATEMENT OF SENATOR MERKLEY

Senator MERKLEY. Thank you, Mr. Chair.

And thank you all for your testimony. I am going to try to keep my questions short because I want to get through several of them.

The first, Dr. Woodcock and Dr. Shuren, I wanted to ask about the issue of developing the Unique Device Identifier, UDI, in the context of medical devices, particularly implantable devices in order to be able to track the results and close the feedback loop.

How important is that to accomplish?

Dr. SHUREN. Unique Device Identifiers are a game-changer. That number now on the device, being able to now either track or to link to information about that device or experience, is critical for things like recall, rapidly identifying the product, more robust adverse event reporting, taking advantage of insurance claims data, electronic health records to identify safety problems.

But also to reduce the cost for some companies on doing their postmarket studies because we can have a more rigorous, robust postmarket surveillance system, and use that information to maybe reduce the evidentiary needs on premarket review.

Senator MERKLEY. This would be included in the Sentinel Postmarketing Studies?

Dr. SHUREN. To actually participate in Sentinel in any meaningful way, we cannot do without a UDI.

Senator MERKLEY. Dr. Woodcock.

Dr. WOODCOCK. Yes, we feel that electronic health records and electronic health data provide tremendous benefit in order to find out what is actually happening with patients with all these new technologies.

The Sentinel program right now has 125 million lives in it. In none of these are the patient data sent to FDA. They stay with the provider, but they are able to perform analyses. We hope to increase that so that we are looking at what most Americans experience, and we would love to have the device program robustly participate in that.

Senator MERKLEY. I believe that the UDI rule is currently stalled at OMB. Any insights on how we can get that rule accomplished in order to have these benefits?

Dr. SHUREN. I will say any kind of help to try to get a UDI system in place would be most welcome by the agency. And I think expressing the importance and maybe even the expectations for having a UDI system in place.

Senator MERKLEY. Maybe we should raise it in a hearing like this and shine a light on it?

Dr. SHUREN. Would be helpful and then some.

Senator MERKLEY. All right. Great, great.

Also, I am working with some other folks to develop a bill, if necessary, to basically put a deadline on getting this rule accomplished so we can try to benefit from this. There are a host of issues associated with this, including the 510(k) process in which a device is approved based on a predicate device that is substantially equivalent.

There is something interesting that occurs, that even if there is a recall of a device in that it can still serve as a predicate for other devices under 510(k).

How is it possible that we allow a device that has been recalled, by the manufacturer, to be utilized as the foundation for other, similar devices to bypass by the regular pre-market approval system?

Dr. SHUREN. That is one challenge in the 510(k) program. I will say the real issues occur very infrequently, and that is where you have a device that has a design flaw that affects safety and effectiveness, and gets recalled. Then a new device comes, and they replicate that design flaw.

Senator MERKLEY. Yes, exactly.

Dr. SHUREN. Under the law, it can be substantially equivalent. We try to work with companies, but oftentimes it is issues about labeling. The burn does not flip the other way to say either the design flaw is not there, so we do not worry, or adequate mitigations have been taken to assure that that device is, in fact, safe and effective.

Senator MERKLEY. It does seem like using a flawed design as a foundation for approving another device under 510(k) is something that we need to wrestle with. It does not make sense to patients who have these implanted devices, and are not too happy to find out the device that was implanted in them, was based on a design that has been recalled.

Dr. SHUREN. Yes, agreed.

Senator MERKLEY. Last, I wanted to raise the issue of drug shortages and drug scalping. My understanding, Dr. Woodcock, is you have not found much evidence of drug scalping. But I keep hearing from practitioners in Oregon of being offered drugs at 10, 20 or even 100 times the price.

So I am trying to figure out, how is it I can hear all these examples from practitioners, but the agency cannot seem to find any evidence that it is a problem?

Dr. WOODCOCK. We have referred to the Department of Justice a compilation of the complaints which is more than 100 drugs in shortage, and we would encourage your constituents to report any of these instances to the FDA, so that we can forward them to the Department of Justice for appropriate investigation.

Senator MERKLEY. OK. We will try to channel as many as possible. It does seem like there is an issue here with middlemen buying up drugs, and then reselling them, and it is such an easy market to corner, when there is a small amount of drugs available in the system.

One of my colleagues referred to the international flow of ingredients, and sometimes that causes shortages that in its moment, that a scalper can capitalize.

I am really hoping we can try to solve this problem because when patients are told, "Well, we are partway through your cancer treatment, and we cannot get the drugs." Or, "We are partway through the cancer treatment and we can only get the drugs at many multiples of what they should cost," something is fundamentally wrong.

Thank you.

The CHAIRMAN. Thank you very much, Senator Merkley.

I understand the votes are going to start at 11:15. Let us see how far we can go. We have Senator Hagan. Senator Blumenthal.

STATEMENT OF SENATOR BLUMENTHAL

Senator BLUMENTHAL. Thank you. Thank you, Mr. Chairman.

If I may ask you, Dr. Woodcock first, how many drugs are in shortage today in the United States?

Dr. WOODCOCK. In 2010, there were 178. We have seen an increasing number. There were 250 shortages tracked in 2011, some of those have been mitigated, but additional ones. So I cannot tell you a summary, but there are over 200 drugs in shortage.

Senator BLUMENTHAL. What is the FDA doing to mitigate those shortages?

Dr. WOODCOCK. We have taken multiple actions, including allowing importation of drugs that are not approved in the United States.

Senator BLUMENTHAL. What is the FDA doing to mitigate those shortages by addressing problems with the manufacturing process?

Dr. WOODCOCK. We work very carefully with manufacturers who are having manufacturing problems to try and keep them in production of the drugs in shortage.

Senator BLUMENTHAL. Have cases of drug shortages and black market issues been referred to the Department of Justice?

Dr. WOODCOCK. Absolutely. Any time we receive any information, we do refer either of price gouging or, of course, when there is an issue of counterfeits.

Senator BLUMENTHAL. Can you tell me which, in the last 3 months, have been referred to the Department of Justice?

Dr. WOODCOCK. We can get that information to you. I do not have it.

Senator BLUMENTHAL. Can you give it to me within the last year?

Dr. WOODCOCK. We certainly can get that to you. Absolutely.

Senator BLUMENTHAL. What steps are being taken to notify the public more expeditiously about those shortages, including the medical community?

Dr. WOODCOCK. We have a Web page. We really try, as much as possible, to both work with the associations and also reach out to the affected communities.

Senator BLUMENTHAL. Have you considered steps that can be taken beyond the way the working group has proposed, or will be proposing within the next few days?

Dr. WOODCOCK. No. I would refer you to the HHS analysis of the root causes of drug shortages by the Assistant Secretary for Planning and Evaluation, which I think has the most in-depth analysis of what caused these shortages and——

Senator BLUMENTHAL. Let me just say that I think that the response of the FDA so far has been inadequate. I have said it before at a hearing, I am not sure whether you were here or not, I feel that working group's proposals are a small step, a baby step, a tiptoe that also fails to address this issue.

I think that the American people will be justly outraged, not just angry and impatient, but outraged when they understand both the causes and the impacts of drug shortages in this country. I will be very disappointed if this Congress fails to do much more than is contemplated right now in addressing these problems in the course of reauthorizing these agreements.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Blumenthal. Again, let me just thank you for your diligence in this area, and your focus on this whole area of the drug shortages, what is causing them, and its impact on our economy and people. I thank you very much.

Senator BLUMENTHAL. Thank you, Mr. Chairman, and I will look forward to receiving that additional information from the FDA.

The CHAIRMAN. Absolutely.

Senator Franken.

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman.

Dr. Shuren, it is good to see you again. Thank you for being so willing to meet with me, and for coming to Minnesota a number of times, and meeting with our medical device industry there.

You and I share a goal of patient safety, and as you acknowledge in your testimony as Director of the office that approves medical devices at the FDA, your job is to make sure that patients are safe.

As you also acknowledged in your testimony, part of patient safety is getting treatments to patients who need them in a timely manner. If a patient with a disease or a condition cannot get a device that would help them stay healthier or even alive, we are failing at keeping that patient safe.

When I talk with medical device manufacturers in Minnesota, they tell me how frustrated they are, that they are developing innovative and potentially lifesaving devices, but they cannot get them

to patients because the FDA has not approved them yet, and you certainly referenced that in your testimony.

I know that you have been working with Minnesota's LifeScience Alley, which just so happens to be the largest life sciences trade association in the Country, on an initiative to develop a regulatory science initiative. I want to thank you, again, for reaching out to Minnesota's biotech industry to work together on this. I hope that initiatives like this one will lead to a real change in the way that you and the industry communicate.

Can you update me on the status of that partnership? And what are your next steps?

The CHAIRMAN. Before you answer, Dr. Shuren, I just want to note that the vote has started at 11:16. It is my intention that after we finish with Senator Franken's round, that we will recess, and then we will come back and start the second panel.

Dr. SHUREN. We have been working with LifeScience Alley to start to identify the specific projects that we would begin to work on together as first steps, and we have actually gotten it to a short list. Our goal is in the coming weeks to finalize on a set of activities that we will be doing jointly together. That will include on the research side. It will include on the education side as well.

Senator FRANKEN. OK.

Dr. Shuren, my bill, the Patient Access to Medical Innovation Act, will help get treatments to patients who need them. As you know, my bill has two provisions.

The first part will help patients with rare diseases get them new and innovative treatments. The second part will remove red tape that keeps the FDA from consulting with the experts in health care and biotechnology which, I think, dovetails with the goals you have with your regulatory science initiative with LifeScience Alley.

I am happy to say that both of these provisions have been included in the bipartisan health committee consensus draft legislation that will be attached to the user fee legislation later this year.

As Director of the office that reviews devices, do you believe that the added flexibility that my bill gives you to consult with experts will help you get safe devices to the market faster? How do you think this flexibility would help you, if that is the case?

Dr. SHUREN. I do think this is helpful. This will allow us to more quickly and with broader scope include critical experts in our pool of special Government employees who can be on our advisory committees, and provide us with advice and recommendations. That is very important to us.

Senator FRANKEN. My other provision will reward innovators who develop devices to treat rare conditions, and Senator Whitehouse talked about the importance of pharmaceuticals for that.

Do you believe that my bill will help patients with rare diseases? And how will it help patients, do you think?

Dr. SHUREN. I do and actually, I want to commend you on this particular provision because you have tried to strike that balance of preserving the incentive already in place for developing devices for pediatric conditions, while extending that incentive for developing devices for other rare conditions.

There are some technical things we would like to work with the committee on for that provision, but this can be an important step

forward for getting and incentivizing development of devices for rare conditions.

Senator FRANKEN. I would be happy to work with you on that and with the Chairman. Thank you both for your testimony.

Now I guess we should go vote.

The CHAIRMAN. The committee will be in recess for about 10 minutes, then we will come back.

Thank you both very, very much. Appreciate it, Dr. Shuren and Dr. Woodcock.

[Recessed.]

The CHAIRMAN. I'll ask our panelists to come up and take their respective seats.

As I said to all of you at the beginning when I made my opening statement, when I introduced you and who you are representing, I thank you for being here. Your statements will all be made a part of the record in their entirety. We will go from left to right and I ask if you would sum up your testimony in 5 minutes or so, we would be most appreciative.

We will start with Dr. David Wheadon, senior vice president for Regulatory Affairs at PhRMA.

Dr. Wheadon, please proceed.

STATEMENT OF DAVID E. WHEADON, M.D., SENIOR VICE PRESIDENT OF SCIENTIFIC AND REGULATORY AFFAIRS, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, WASHINGTON, DC

Dr. WHEADON. Thank you. Chairman Harkin, Ranking Member Enzi, members of the committee, good morning.

I am David Wheadon, senior vice president of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, better known as, 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 authorization of the Biosimilars User Fee Act, BsUFA.

The PDUFA–V performance goals letter is the result of extensive negotiations between the U.S. Food and Drug Administration 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 in negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers, and academia.

PhRMA, as the representative of the country's leading pharmaceutical research and biotechnology companies, strongly supports the original intent and 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 and urges Congress to reauthorize PDUFA in a timely manner, based on the PDUFA–V agreement.

This agreement will provide FDA with the resources and tools required to further enhance the timeliness, completeness, and efficiency of the drug review process.

As you have heard this morning, failure to authorize 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 with debilitation diseases.

PDUFA–V will improve the review process for new molecular entity drug and biologic applications, which will be particularly significant for patients because NME's are novel compounds that have the potential to address unmet medical needs in advanced patient care. The enhanced NME review process addresses the increasing complexity of reviewing new drug applications and biological license applications, and provides for increased communication between FDA and drug sponsors prior to and during the drug review process.

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. 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.

Several new provisions in the PDUFA–V performance goal letter 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.

Provisions to enhance FDA's regulatory review capabilities include, but are not limited to, 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 providing FDA with the necessary regulatory flexibility to encourage and advance research into novel treatments for patients with significant unmet needs today. And forming a public process to help standardize Risk Evaluation and Mitigation Strategies, or REMS, with the intent to assess and reduce burden on healthcare providers and patients.

PDUFA has advanced public health by accelerating the availability of innovative medicines to patients who are helping to insure patient safety. 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 urges 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.

I will just briefly comment on BsUFA, but I know my colleague will be focusing on that. But the BsUFA performance goals are consistent with congressional intent to create a unique user fee pro-

gram to meet the needs of biosimilar product applicants, and to provide FDA with the means necessary to build, essentially from scratch, its capacity for science-based review for biosimilar applications.

Among the key aspects of the proposed BsUFA performance goals is the expectation for FDA in fiscal year 2013 to review and act on 70 percent of original biosimilar application submissions within 10 months of receipt, and to review and act on 70 percent of resubmissions within 6 months of receipt. As the agency's review capacity for biosimilar products develops, review performance goals will gradually increase.

In summary, PhRMA and our managed member companies are committed to working closely with FDA and all stakeholders to ensure the continued success of PDUFA in bringing safe, effective, innovative medicines forward to address unmet medical needs for all patients.

PhRMA stands ready to work with the FDA and other stakeholders in establishing a science-based approach to the development and review of biosimilar and interchangeable biological products.

We therefore urge Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA–V agreement and to authorize BsUFA with congressional appropriations allocated in support of this program for fiscal years 2013 through 2017.

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

[The prepared statement of Dr. Wheadon follows:]

PREPARED STATEMENT OF DAVID E. WHEADON, M.D.

SUMMARY

The Prescription Drug User Fee Act (PDUFA) has been a great success for patients since its initial passage in 1992. The PDUFA user fee program provides FDA with the additional staffing and resources it needs to significantly reduce the timeframe for the review of new medicines, while protecting public health by assuring the safety of these products.

- The PDUFA–V performance goals letter is the result of extensive negotiations between the FDA and the innovative biopharmaceutical industry. FDA's process for negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers and academia.
- A number of important new commitments are detailed in the PDUFA–V performance goals letter, including provisions to make the regulatory review of new medicines more efficient and timely, advance regulatory science and modernize drug development, improve benefit/risk decisionmaking, and further strengthen FDA's focus on patient safety.
- PhRMA urges Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA–V performance goals and to minimize inclusion of additional provisions that may distract from the Act's original intent—faster access to innovative medicines while preserving and strengthening the FDA's high standards for safety, efficacy and quality.
- Failure to reauthorize PDUFA in a timely manner would not only have an extraordinarily disruptive effect on the FDA and impede patients' access to new and innovative treatments, but such a failure would also endanger biopharmaceutical innovation.

The Biologics Price Competition and Innovation Act of 2009 (BPCIA) established an abbreviated pathway for biosimilar products and interchangeable biological products. PhRMA was a participant in the technical negotiations with the FDA that, together with input from patient and healthcare provider groups, resulted in the Biosimilars User Fee Act (BsUFA)performance goals letter.

• The BsUFA performance goals are consistent with congressional intent to create a unique user fee program to meet the needs of biosimilar product applicants, and to provide FDA with the means necessary to build, essentially from scratch, its capacity for science-based review of biosimilar applications.
• PhRMA believes that the review process for biosimilar and interchangeable biological products must be scientifically rigorous, timely, and above all, protective of patient safety. Achieving these objectives will require a clear and formalized regulatory pathway for biosimilar products, quality standards equal to standards for innovative products, and adequate preclinical and clinical testing to ensure that biosimilars are both safe and effective.
• PhRMA urges Congress to authorize BsUFA with congressional appropriations allocated in support of this program for fiscal years 2013–17.

Chairman Harkin, Ranking Member Enzi, members of the committee, good morning. 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 authorization of the Biosimilars User Fee Act (BsUFA).

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 United States 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 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. 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

[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.

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 decisionmaking, and to further strengthen FDA's focus on patient safety.

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 decisionmaking, 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.

AUTHORIZATION OF A USER FEE PROGRAM FOR BIOSIMILAR BIOLOGICAL PRODUCTS UNDER THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (BSUFA)

An abbreviated approval pathway for biosimilar products and interchangeable biological products was established in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) and PhRMA has been supportive of FDA's ongoing efforts to implement BPCIA in a manner that ensures patient safety and encourages biopharmaceutical innovation. PhRMA was a participant in the technical negotiations with the U.S. Food and Drug Administration (FDA) that, together with input from patient and healthcare provider groups, resulted in the Biosimilars User Fee Act (BsUFA) performance goals letter.

The BsUFA FDA performance goals are consistent with congressional intent to create a unique user fee program to meet the needs of biosimilar product applicants, and to provide FDA with the means necessary to build, essentially from scratch, its capacity for science-based review of biosimilar applications. PhRMA believes that the BsUFA performance goals will benefit patient safety and public health as biosimilar products will be required to meet FDA's high standards for safety, purity, and potency.

Several of PhRMA's member companies for many years have been actively engaged in the development of innovative biological products. In addition, some of PhRMA's member companies have expressed their intent to develop biosimilar products. PhRMA therefore supports the development of a robust user fee program for biosimilar products to provide FDA with the resources needed to review biosimilars without diverting resources from the review of innovative medicines. PhRMA is further supportive of the appropriation of congressional funds for this purpose, a feature common to existing user fee programs, to ensure that user fees supplement, rather than replace, appropriations.

PhRMA believes that the review process for biosimilar and interchangeable biological products must be scientifically rigorous, timely, and above all, protective of patient safety. Achieving these objectives will require a clear and formalized regulatory pathway for biosimilar products, quality standards that meet standards for innovative products, and adequate preclinical and clinical testing to ensure that biosimilars are both safe and effective.

PhRMA recognizes that, for the purpose of this first authorization, the biosimilar user fee program must be structured differently from other user fee programs. It will be necessary, for example, to collect fees earlier in the biological product development process, until fees from licensing applications can provide sufficient ongoing revenues to support the Agency's activities. It must be understood, however, that the proposed user fee program for biosimilar products—and, in particular, the provision for payment of a portion of the application fee at the time of an Investigational New Drug (IND) submission and yearly thereafter—is a stop-gap measure, subject to review at the time of BsUFA reauthorization in 2017.

Among the key aspects of FDA's proposed BsUFA performance goals is the expectation for FDA, in fiscal year 2013, to review and act on 70 percent of original biosimilar application submissions within 10 months of receipt and to review and act on 70 percent of resubmissions within 6 months of receipt. As the Agency's review capacity for biosimilar products develops, review performance goals will gradually increase.

The BsUFA performance goals further provide for specific FDA/sponsor meetings to facilitate the biosimilars development phase. This provision includes a special protocol assessment mechanism for clinical study protocols that are intended to establish biosimilarity and/or interchangeability with a reference biological product, to

help ensure that the study design is adequate to meet scientific and regulatory requirements for approval.

The proposal also calls for FDA to issue guidance on procedures for meetings between the Agency and sponsor prior to submission of a biosimilar licensing application, and PhRMA urges the Agency to accelerate its guidance development in this area. Eventually, the biosimilar application process should be codified in regulations similar to all other approval pathways.

Additionally, user fees will be applied to enhance patient safety through implementation of measures to reduce medication errors related to similar sounding proprietary names, unclear labeling, and confusing package design.

PhRMA supports the proposed BsUFA performance goals agreement as a means of advancing public health by making adequate resources available to FDA to build a capacity for regulatory review of biosimilar products, consistent with the Agency's high standards for patient safety and scientific rigor.

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. Additionally, PhRMA stands ready to work with the FDA and other stakeholders in establishing a science-based approach to the development and review of biosimilar and interchangeable biological products. PhRMA therefore urges Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA–V agreement and to authorize BsUFA with congressional appropriations allocated in support of this program for fiscal years 2013 through 2017.

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

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

Now we turn to Miss Radcliffe representing the Biotechnology Industry Organization.

Miss Radcliffe, welcome.

STATEMENT OF SARA RADCLIFFE, EXECUTIVE VICE PRESIDENT, HEALTH, BIOTECHNOLOGY INDUSTRY ORGANIZATION, WASHINGTON, DC

Ms. RADCLIFFE. Thank you very much.

Chairman Harkin, Ranking Member Enzi, 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. In that role, I had the opportunity to manage BIO's involved in the Biosimilars User Fee, or BsUFA, technical discussions with FDA as well as lead BIO's engagement in the Prescription Drug User Fee Act 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 healthcare needs, curing disease, reducing costs, increasing quality, and insuring that people enjoy not only longer lives, but also better and more productive lives.

I am here today primarily to express BIO's strong support for the authorization of the biosimilars user fee program as part of FDA's ongoing implementation of a well-constructed, science-based pathway with the approval of biosimilar biological products that protects patient safety and preserves incentives to innovate.

Throughout both the legislative consideration of the Biologics Price Competition and Innovation Act of 2009 and ongoing FDA implementation of the pathway, BIO articulated a number of principles that will promote the development of an effective regulatory

framework for biosimilar biological products including: that patient safety be insured, that the scientific differences between drugs and biologics be recognized, that incentives for innovation be preserved, that transparent statutory and regulatory processes be established and followed, and that FDA would continue to prioritize the review and approval of innovative therapies and cures.

BIO believes that the proposed standalone user fee program is consistent with these principles. BsUFA will provide FDA with dedicated user fee resources and review capacity to facilitate the development and evaluation of biosimilar, biological products while also continuing to prioritize the review of innovative drugs and biologics under PDUFA.

I would like to mention a few key features of the BsUFA program. First, the biosimilars user fee program establishes a unique product development fee, which is ultimately deducted from the sponsor's application fee. Because there is currently no established biosimilar industry to form a stable funding source for activities that occur before submission of applications, it is important to front load the fees through this product development fee so that the agency has resources available to meet with sponsors during development to provide scientific advice and feedback.

We note, however, that this situation with respect to biosimilar biological products should not establish any precedent for investigational new drug or IND fees under the PDUFA program. Additionally, an IND-associated fee should sunset permanently in fiscal year 2018 when both PDUFA and this new user fee program would sunset.

PDUFA also promotes robust postmarket safety for biosimilar biological products by establishing a lifecycle approach to product evaluation and directing resources to FDA's postmarket pharmaco vigilance activities in alignment with approach to drug safety that has been adopted by innovative sponsors.

BIO also recognizes that historically most FDA user fee programs have been established on a preexisting base of appropriations. However, only modest appropriations are currently allocated to biosimilars review processes. To facilitate an equitable balance of fees and appropriations, FDA and industry support a trigger provision similar to the established appropriations triggers in other user fee programs that would ensure FDA allocates at least $20 million per year to the program.

BIO encourages Congress to recognize the importance of a well-resourced and viable biosimilars pathway at FDA, and we request that adequate new funding be appropriated for the program.

I would also like to address briefly the Prescription Drug User Fee Act or PDUFA reauthorization. We have addressed the elements of the PDUFA–V technical agreement in detail in our written testimony. In short, BIO believes that the PDUFA program represents a critical element of our Nation's overall innovation ecosystem. The set of PDUFA–V enhancements that were agreed by FDA, BIO, and PhRMA seek to reinforce FDA's review program and get back to basics for patients.

Timely PDUFA reauthorization will enhance the drug development and review process through increased transparency in scientific dialog, advanced regulatory science, strengthen postmarket

surveillance, and help establish best practices for timely interactive dialog between sponsors and the agency during drug development. Most importantly, our hope is that PDUFA–V will provide patients and doctors with earlier access to important new therapies.

In conclusion, 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. Both user fee programs, BsUFA and PDUFA, will enhance FDA's ability to protect and promote the public health, and we strongly encourage Congress to enact them in a timely manner.

Thank you.

[The prepared statement of Ms. Radcliffe follows:]

PREPARED STATEMENT OF SARA RADCLIFFE

SUMMARY

BIO supports swift enactment of the Biosimilars User Fee Agreement (BsUFA). The funding and goals contained in this proposal, along with a well-constructed, science-based, transparent pathway for the approval of biosimilar products, will ensure that FDA can facilitate the development and evaluation of biosimilars products.

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

Additionally, BsUFA promotes robust post-market safety for biosimilar products by establishing a life-cycle approach to product evaluation and directing resources to FDA's post-market pharmacovigilance activities. Because biologics are complex and challenging to characterize, and the nature of a biologic is closely dependent on the starting materials and processes used to make that product, minor changes made by a manufacturer to starting materials or to manufacturing processes can lead to changes in the product that may not be detectable by current technologies. Therefore, a carefully designed pharmacovigilance effort is important.

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

The biosimilars user fee program also establishes a unique biosimilar product development fee, which is ultimately deducted from the sponsor's application fee. The assessment of a product development fee is unique to this situation with respect to biosimilar products and should not establish any precedent for investigational new drug (IND) fees under the PDUFA program. Additionally, any IND-associated fee should sunset permanently in fiscal year 2018 when both PDUFA and this new user fee program would sunset.

A key to the success and the future of the U.S. biotechnology industry is a reliable, predictable, and science-based regulatory environment, and the PDUFA program represents an important element of our Nation's overall innovation eco-system. While establishing a sound BsUFA was a priority for BIO, so too is reauthorizing PDUFA. The principles which guided BIO in our technical discussions with FDA regarding PDUFA reauthorization 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 prin-

ciples in mind, BIO, PhRMA, 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 have also been informed by an unprecedented level of public input through workshops, meetings, and stakeholder outreach, which further strengthened the technical agreement.

Under the PDUFA–V agreement, industry has reinforced its commitment to a well-funded drugs and biologics review 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 fiscal year 2012 requested levels.

Finally, it is critical for PDUFA to be reauthorized well in advance of PDUFA–IV's expiration in September 2012, to avoid a reduction in force at the FDA. Even the threat of a downsizing at the FDA would be devastating to the Agency's public health mission and its ability to review new drugs and biologics.

Chairman Harkin, Ranking Member Enzi, 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 have had the opportunity to manage BIO's involvement in the biosimilars user fee (BsUFA) technical discussions, as well as lead BIO's engagement in the Prescription Drug User Fee Act (PDUFA) technical discussions with the Food and Drug Administration (FDA).

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.

I am here today to express BIO's support for the establishment of the biosimilars user fee program as part of FDA's ongoing implementation of a well-constructed, science-based pathway for the approval of biosimilar products that protects patient safety and preserves incentives to innovate. BsUFA will provide FDA with the resources and capacity to facilitate the development and evaluation of biosimilars products, while also continuing to prioritize the review of innovative drugs and biologics under PDUFA so that safe and effective new treatments—many for currently untreatable and serious diseases—can be made readily available to patients.

BIO also supports timely reauthorization of PDUFA, which we believe will enhance the drug development and review process through increased transparency and scientific dialog, advance regulatory science, and strengthen post-market surveillance. Most importantly, our hope is that PDUFA–V will provide patients and doctors with earlier access to important new therapies.

I. 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.

The establishment of a stand-alone, independent biosimilars user fee program is consistent with congressional intent and precedent established under other user fee

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

Additionally, BsUFA promotes robust post-market safety for biosimilar products by establishing a life-cycle approach to product evaluation and directing resources to FDA's post-market pharmacovigilance activities. Because biologics are complex and challenging to characterize, and the nature of a biologic is closely dependent on the starting materials and processes used to make that product, minor changes made by a manufacturer to starting materials or to manufacturing processes can lead to changes in the product that may not be detectable by current technologies. Therefore, a carefully designed pharmacovigilance effort is important.

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

The biosimilars user fee program also establishes a unique biosimilar product development fee, which is ultimately deducted from the sponsor's application fee. Because there is no established biosimilars industry, facility base, and product base to form a stable funding source for activities that occur before submission of applications, it is important to "front-load" the fees through the product development fee so that the agency has resources available to meet with sponsors during development to provide scientific advice and feedback. It should be noted, however, that the assessment of a product development fee is unique to this situation with respect to biosimilar products and should not establish any precedent for investigational new drug (IND) fees under the PDUFA program. Additionally, any IND-associated fee should sunset permanently in fiscal year 2018 when both PDUFA and this new user fee program would sunset.

II. PDUFA–V: GETTING BACK TO BASICS FOR PATIENTS

A key to the success and the future of the U.S. biotechnology industry is a reliable, predictable, and science-based regulatory environment, and the PDUFA program represents an important element of our Nation's overall innovation eco-system. Since 1992 Congress, FDA, and the biopharmaceutical industry have supported this carefully structured user fee program to help fund FDA's human drug review activities. The program has contributed to the approval of more than 1,200 new medicines and, initially, reduced review times for the newest, most innovative drugs by more than a year.

While establishing a sound BsUFA was a priority for BIO, so too is reauthorizing PDUFA. The principles which guided BIO in our technical discussions with FDA regarding PDUFA reauthorization 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, BIO, PhRMA, 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 have also 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 percent of all NME applications submitted to FDA are ultimately approved, but fewer than half are approved on the first submission.[1] Sponsors and FDA can and must do better for patients. By strengthening scientific dialog and transparency between

[1] Fiscal year 2010 PDUFA Performance Report, p. 4, *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf*.

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 dialog 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 2-month validation period preceding 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.

FDA's recent report on driving biomedical innovation highlights that "the private sector is the engine of innovation, and much of this innovation begins with small business."[2] Indeed, many small biotechnology companies operate on the cutting edge of biomedical science to develop new therapies for devastating diseases. Yet we must acknowledge that 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.

Additionally, independent reports commissioned by FDA have demonstrated that enhanced communication during drug development ultimately results in higher quality applications, which can improve efficiency for FDA reviewers.[3]

BIO fully supports the PDUFA–V proposal to promote innovation through enhanced communication between FDA and Sponsors during drug development, which will establish best practices for this type of interactive dialog, train staff on communication practices, and provide the Agency with additional staff capacity to respond to sponsor inquiries in a timely manner.

• **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 the application of new tools for rare disease drug development, flexibility with regard to creative study designs and new endpoints, and greater utilization of biomarkers and patient-reported outcome measures, 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 drugs and biologics review program that supports sound, science-based regulation consistent with FDA's public health mission. However, user fees are in-

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[2] *FDA, Driving Biomedical Innovation: Initiatives for Improving Products for Patients*, October 2011, *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM274464.pdf*.

[3] Booz Allen Hamilton, *Independent Evaluation of FDA's First Cycle Review Performance—Final Report*. July 2008, *http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127117.htm*.

tended 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 fiscal year 2012 requested levels.

Additionally, it is critical for PDUFA to be reauthorized well in advance of PDUFA–IV's expiration in September 2012, to avoid a reduction in force at the FDA. Even the threat of a downsizing at the FDA would be devastating to the Agency's public health mission and its ability to review new drugs and biologics.

BIO looks forward to working with Congress and FDA to fully implement these enhancements under PDUFA–V.

III. CONCLUSION

In conclusion, BIO supports enactment of the proposed biosimilars user fee program, which will provide FDA with adequate resources and promote predictability in FDA's biosimilars review process, while continuing to promote the development and evaluation of innovative therapies for unmet medical needs under PDUFA. Both user fee programs will enhance FDA's ability to protect and promote the public health, and we encourage Congress to enact both legislative provisions in a timely manner.

The CHAIRMAN. Thank you very much, Miss Radcliffe.

Senator ENZI. Mr. Chairman, I apologize.

I am going to leave. I want to thank Dr. Woodcock and Dr. Shuren for staying to hear this testimony, and my staff will be staying to hear the testimony, and I will have questions to submit.

The CHAIRMAN. I appreciate that.

Senator ENZI. Thank you.

The CHAIRMAN. Thank you very much, Senator Enzi.

I thank you very much, Miss Radcliffe.

Now we turn to David Gaugh, the vice president for Regulatory Sciences at the Generic Pharmaceutical Association. Did I pronounce that name right?

Mr. GAUGH. Gaugh.

The CHAIRMAN. Gaugh.

Mr. GAUGH. Yes.

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

STATEMENT OF DAVID R. GAUGH, R.PH., VICE PRESIDENT FOR REGULATORY SCIENCES, GENERIC PHARMACEUTICAL ASSOCIATION, WASHINGTON, DC

Mr. GAUGH. Good morning, Chairman Harkin, Ranking Member Enzi, and members of the committee.

Thank you for asking me to participate in this timely and important hearing. I am David Gaugh, vice president for Regulatory Sciences at the Generic Pharmaceutical Association and a licensed pharmacist.

GPhA represents the manufacturers, distributors, and finished dose generic pharmaceuticals, both pharmaceutical chemicals and the suppliers of goods and services to the generic industry. Generic pharmaceuticals account for 80 percent of all prescriptions dispensed in the United States, but consumed as 25 percent of the total drug spending for prescription medicines.

I would like to begin today by commending the committee for your continued focus on this important issue that we are going to examine today. As someone who has worked in and around the generic industry for more than two decades, I witnessed firsthand the industry's remarkable growth and the vital role it plays in the lives of Americans every day.

This growth in the generic industry has also served to underscore the critically important role of the Food and Drug Administration. As I will highlight, the levels of cooperation between the industry and the FDA have never been greater, and it is our hope that this collaboration will continue, and extend throughout all of the interactions with the agency.

However, the agency remains underfunded and the responsibility of insuring access to safe and affordable medicines is shared by one that rests on the entire pharmaceutical industry and 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.

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 6 months that were required by Hatch-Waxman. Unfortunately, this backlog keeps safe, low-cost generics off the market and reduces competition that may drive drug 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 generic drugs.

GPhA also recognizes, however, that while providing early access to effective medicines is critical and the key aim of all the existing user fee programs, an equally important pillar of FDA and industry mission is insuring drug safety. This is why GDUFA takes the unprecedented step of holding all players contributing to the generic U.S. drug system, foreign and domestic, to the same inspection standards, and enhances FDA's ability to identify and require the registration of active pharmaceutical ingredient and finished dose foreign manufacturers involved in each generic drug product sold in the United States.

It is paramount that as we work to shape the future of our country's generic industry, we also work to bring the FDA into the 21st century, and ensure that the agency's authority to achieve its mission in this global age are up to date.

This is further exemplified by the other user fee program we will discuss today for generic biologic drugs or biosimilars. Biologic medicines are often the only lifesaving treatment 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 the reach of many patients.

During biosimilar user fee negotiations, GPhA expressed its support for user fees 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 the user fee program by gaining a higher degree of certainty and timeliness in the applications that are reviewed.

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 and reviewing the approval of these important drugs.

By designing both of these user fee programs to spread fees across multiple stakeholders and sources to keep individual amounts as low as possible, the programs will help assure that the American consumers continue to receive significant cost savings from generics that, over the past 12 years, have provided more than $1 trillion in savings to the national healthcare system.

It is also important to emphasize that the funding provided by both of these user fee agreements is in addition to, and not a substitute for, congressional appropriations.

In conclusion, Mr. Chairman, this is truly an historic time for GPhA, the user fee proposals are the culmination of months of negotiation between the FDA and the 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 the FDA and industry, and without changes to the underlying agreements.

Thank you, and I will take any questions.

[The prepared statement of Mr. Gaugh follows:]

PREPARED STATEMENT OF DAVID R. GAUGH, R.PH.

SUMMARY

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 United States but consume just 25 percent of the total drug spending.

Thanks to the efforts of the Food and Drug Administration (FDA), the U.S. drug supply remains the safest 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, through the negotiation of two new user fee agreements, has stepped up to help provide the FDA with additional resources to address the ongoing challenges faced by the agency. The Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BsUFA) will help ensure U.S. drug safety, establish a more level playing field among all participants in the U.S. pharmaceutical supply chain, and make certain that all Americans receive timely access to safe, effective and affordable generic drugs. We urge the committee to approve GDUFA and BsUFA as negotiated by FDA and industry 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

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. The Generic Drug User Fee Act (GDUFA) will help alleviate the backlog and expedite consumer access to generic drugs, while also enhancing drug quality and safety. FDA will receive $299 million per year over the 5-year GDUFA program, or about $1.5 billion in total. The new user fee program will also establish performance goals for the FDA. The agreement's performance goals call for FDA to complete, by the end of year five, the review of 90 percent of all ANDAs that are pending on October 1, 2012—effectively eliminating the current application backlog. By the end of the program's fifth year, GDUFA calls on the FDA to review 90 percent of ANDAs within 10 months after they are submitted—almost 2 years faster than today's average review time. GDUFA also takes the unprecedented step of holding all players contributing to the U.S. generic drug system, foreign or domestic, to the same inspection standards, and

enhances FDA's ability to identify and require the registration of API and finished dosage form manufacturers involved in each generic drug product sold in the United States.

BIOSIMILAR USER FEE ACT

The 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.

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

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 United States, but consume just 25 percent of the total drug spending for prescription medicines.

According to a recent 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 United States, 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.

This growth in the generic industry has also served to underscore the critically important role of the Food and Drug Administration (FDA). As I will highlight, the level of cooperation between industry and the FDA has never been greater. The two historic user fee agreements 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 new and complex technologies.

Throughout much of last year, GPhA and our member companies worked closely with the FDA to negotiate two separate user fee programs designed to help the agency obtain additional resources to ensure all participants in the U.S. generic drug system, whether U.S.-based or foreign, comply with all of our country's strict quality standards. Most importantly, the programs will make certain that all Ameri-

cans receive timely access to safe, effective and affordable generic drugs. Let me provide some more details.

LANDMARK USER FEE PROGRAMS WILL PROVIDE ADDITIONAL RESOURCES

Currently, more than 2,700 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, more than five times longer than the statutory 6-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 5-year GDUFA program, or about $1.5 billion in total. Of that funding, 80 percent, or about $240 million, will come from finished-dose manufacturers, and the remaining 20 percent will be paid by manufacturers of active pharmaceutical ingredients. Thirty percent of the funding will stem from application fees and 70 percent will be derived from fees on manufacturing sites, or facility fees.

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

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

In addition, by the end of the program's fifth year, GDUFA calls on the FDA to review 90 percent of ANDAs within 10 months after they are submitted—almost 2 years faster than today's average review time.

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

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

GPhA has long-maintained that, in light of this increasing globalization and with nearly 40 percent of all the prescription drugs in the United States 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 9 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 United States. The program will significantly improve the resources the FDA has to do this important work, ensuring that it can be done with increasing speed, but without any sacrifice to today's high quality standards.

It is 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 calls for the agency, by the end of the program's fifth year, to review 90 percent of the original biosimilar applications it receives within 10 months of their submission.

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

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

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

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. As the user fee legislation moves forward, we urge Congress to address additional areas—currently outside the scope of the user fee acts—that would further increase access to safe and effective generic medicines.

For example, a concern related to Hatch-Waxman that warrants Congress' attention involves the law's "Section viii" process. Under a Federal court's interpretation of current law, brand-name drug manufacturers are able to block generic competition by providing the FDA with misleading and overbroad descriptions of their patents.

While "Section viii" allows generic manufacturers to market their products for FDA-approved uses not covered by any patent, brand manufacturers have circumvented this process by changing their product's "use code"—a description of the

patent required to be filed by the FDA. Because the FDA is not institutionally equipped to question brands' use codes by reading their patents, the agency has had no choice but to deny the approval of generic competition in such cases. And the Federal Circuit held that there is no judicial remedy for the problem. Though the U.S. Supreme Court is now considering reversing that ruling, clarity of the legislative language is needed and would be beneficial even if the appellate ruling is overturned.

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

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

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

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

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

CONCLUSION

In conclusion, Mr. Chairman, this truly is 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.

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

Next, we have Dr. David Nexon, senior executive vice president for the Advanced Medical Technology Association, an association representing manufacturers of medical devices and diagnostics.

We also thank the representatives of the Medical Device Manufacturers Association and the Medical Imaging Technology Association who have coordinated with Dr. Nexon regarding his testimony, so that it will reflect the full scope of the medical device industry.

Quite frankly, it is rather a shock to my system to see Dr. Nexon sitting there rather than here. I started out way down there, Michael, down at that end and Dr. Nexon was our traffic cop back here, but he always treated me well, and I appreciate it very much.

Dr. Nexon, welcome back to the committee on this side of the podium, I guess.

STATEMENT OF DAVID NEXON, Ph.D., SENIOR EXECUTIVE VICE PRESIDENT, ADVANCED MEDICAL TECHNOLOGY ASSOCIATION, WASHINGTON, DC

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

It is quite a pleasure to be back with the HELP committee, although I must confess, as you pointed out, it feels a little strange to be on this side of the witness table.

As many of you know, our industry has been a true American success story for patients and for the U.S. economy. America's medical technology industry truly leads the world, but our leadership is slipping.

One key reason, and perhaps the most important reason that our leadership is slipping is the significant decline we have seen in FDA efficiency and consistency in recent years. I am pleased that the FDA leadership and Dr. Shuren have recognized the need to vigorously address the issues affecting the device center, and we heard from Dr. Shuren this morning about a number of steps that they are taking to turn the situation around.

We believe that 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 patients.

The user fee agreement builds the conditions for success in a number of major ways. For the first time ever, this user fee agreement establishes average total time goals for FDA product review. All previous agreements have set their goals in terms of time on the FDA clock. But what matters to industry and patients are the actual days on the calendar that it takes to get a product from submission to final decision by FDA. By setting in place this new goal, efforts will be focused on the metric that is truly most important to everyone concerned.

Second, the agreement also established improved goals for time on the FDA clock. These goals are a key management tool for FDA and they work in concert with the total time goal to produce better performance that either could achieve alone.

Third, the agreement includes process standards that we anticipate will also improve the review process. These include meaningful presubmission interactions between FDA and companies. Agreements reached in these interactions will be binding unless, of course, new information arises that requires a change to protect the public health.

A mandatory substantive interaction between FDA and the company midway through the review process is also included in the agreement. This will assure that both companies and the FDA identify any deficiencies in the application early so that they can be corrected promptly.

The new procedure that we call "no submission left behind," that Dr. Shuren also referenced, will be instituted so that if the FDA time target is missed, the company and the FDA will meet to work out a schedule for resolving the remaining issues so that the submission does not go to the bottom of the pile and not get looked at again.

Fourth, the agreement provides for greater accountability. Greater accountability means that FDA's success under this agreement will be transparent to FDA, 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 a wide variety of key metrics that both FDA and industry agree 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 opportunities for improvement.

Finally, to give FDA additional tools to meet the new goals, the agreement provides $595 million in user fees over the life of the agreement. 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 FTE's and the vast majority of these new FTE's will put in place where they are needed the most as additional reviewers. This coupled with the additional supervisors who are being hired this year should lead to more consistency and speed in the review process.

Of course, and I want to emphasize this, 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 has 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 critically important. Patients are really depending on all of us.

Finally, I should note that a number of legislative proposals have been introduced with the goal of improving the FDA's operations. We are appreciative of the efforts by all members who seek to give the FDA the tools and structure it needs to succeed. At the same time, I do want to emphasize that we are strongly committed to the user fee agreement as negotiated and we do not support any proposals that would change the terms of the agreement or undermine its goals.

Just as this new user fee agreement has the potential to help FDA move in a very positive direction for patients and industries, the view I have emphasized, Mr. Chairman, and as Ranking Member Enzi emphasized, failure to reauthorize this program in a timely way would really be catastrophic for the FDA, for industry, and for patients.

I thank the committee for the opportunity to testify and we strongly support your efforts and urge the committee to do what it is we know you want to do, which is to promptly reauthorize this program, which is so critical to patients, to the FDA, and to our industry.

Thank you very much.

[The prepared statement of Mr. Nexon follows:]

PREPARED STATEMENT OF DAVID NEXON, PH.D.

• 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 negations, 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 pre-submission 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.
• Last, to give FDA additional tools to meet the new goals, the agreement provides $595 million in user fees for 2013–17.
• 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.

Thank you Chairman Harkin, Ranking Member Enzi, and members of the committee for the opportunity to testify today.

My name is David Nexon, and I am senior executive vice president of the Advanced Medical Technology Association (AdvaMed). 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, MDMA, and 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 and our employees, so that the total numbers generated by our industry exceeds 2 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 percent, adding 73,000 jobs. During the recession, between 2007 and

2008, MedTech employment dropped 1.1 percent, compared to 4.4 percent for manufacturing as a whole.

Our industry is heavily skewed toward small companies—the kind of companies that begin with a doctor, and engineer, and an idea to improve patient care. Almost two-thirds of the 7,000 medical technology firms in the United States 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 3 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 percent.

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 PriceWaterhouseCoopers 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 decisionmaking, 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. While the FDA has consistently maintained a strong record of assuring the 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.

I am pleased to be able to report that after extensive negotiations, the user fee agreement between FDA and industry has been reached and is now awaiting your action. We believe this agreement has the potential to help achieve meaningful change 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 our industry representatives just concluded with the agency 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 of major ways.

TOTAL TIME GOAL

For the first time ever, this user fee agreement establishes average total time goals 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 meeting the goals for 510(k) submissions, the total time from submission to final decision increased 43 percent between the average for 2003–7 and 2010. Of course, what matters to companies and patients is not an artificial construct like time on the FDA clock, but the time it actually takes to get a decision from FDA.

FDA, of course, often has legitimate questions about an application and it cannot control the amount of time it takes for a sponsor to respond to questions about any individual application. But all sponsors want to submit applications that meet FDA standards, and 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. We refer to this new standard as a shared performance goal, because industry also has an obligation to submit good applications. Additionally, FDA will have new authority to decline to begin review of an application that is obviously deficient when it is submitted.

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, for PMAs receiving panel reviews—which tend to be the most innovative products. By the end of this new agreement, 90 percent of PMA products will receive a decision within 320 days. 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 standards 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.

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.

A new procedure that we call "no submission left behind" will be instituted, so that if the FDA time target is missed, the company and the FDA will meet to work out a schedule for resolving remaining issues, so that the submission doesn't go to the bottom of the pile.

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 opportunities for improvement.

APPROPRIATE RESOURCES

Finally, to give FDA additional tools to meet the new goals, the agreement provides $595 million in user fees for 2013–17. 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 move 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 above, 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.

CONCLUSION

Finally, I should note that 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. 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.

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.

I thank the committee for the opportunity to testify and urge you to act promptly to reauthorize this program which is so critical to patients, to the FDA and to our industry.

The CHAIRMAN. David, thank you very much, again and thank you for your 20 years of service to this committee too.

Mr. NEXON. Thank you, Mr. Chairman.

The CHAIRMAN. Next, we turn to Allan Coukell, the director of Medical Programs at The Pew Health Group. In his current role, he supervises programs related to pharmaceutical supply chain safety, antibiotic development and stewardship, and conflict of interest issues.

Mr. Coukell, welcome to the committee. Please proceed.

STATEMENT OF ALLAN COUKELL, B.SC.PHARM., DIRECTOR OF MEDICAL PROGRAMS, THE PEW CHARITABLE TRUSTS, WASHINGTON, DC

Mr. COUKELL. Mr. Chairman and members of the committee, thank you for the opportunity to testify.

My name is Allan Coukell and I direct medical programs for The Pew Health Group, which conducts research and analysis aimed at improving the safety and well-being of American consumers. As you mentioned, Pew has a number of initiatives related to drugs, medical devices, and FDA.

Today, I would like to talk about how the user fee agreements can promote innovation and help to ensure the safety and effectiveness of medical products with the ultimate goal of improving health.

Since 1992, PDUFA fees have given FDA significant and sustained resources that allow the agency to review new products

quickly. Indeed, 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.

PDUFA also established an accelerated review process for drugs that offer major advances or provide treatment where no adequate therapy exists, and FDA devotes extra resources to reviewing those drugs.

This issue is especially important to Pew's Antibiotics and Innovation Project, which is working to promote the development of new antibiotics needed to treat serious and life threatening bacterial infections.

Of the last 11 new antibiotics approved, four received priority review and that meant faster approvals for drugs for pneumonia, serious skin infections, and for C. difficile diarrhea, which causes 14,000 U.S. deaths each year.

The Medical Device User Fee Program is similarly important, and we are asking Congress to swiftly reauthorize it. The fees that FDA collects under MDUFA would add 200 new staff and nearly $600 million for the review of device applications, and these new funds are important.

Pew recently commissioned an analysis of personnel at FDA showing that the Device Center has higher attrition rates than the centers for drugs and biologics, or the office of regulatory affairs. Nearly 10 percent of staff in CDRH left in fiscal year 2010, and the majority of device staff reported that they did not have sufficient resources to get their job done. To function effectively, CDRH must have adequate funding.

But it is critical to remember 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. While more challenging to measure than review times, improving health is the ultimate goal of the FDA.

User fees primarily support review of new products, but some funds are available to support drug safety activities. Five years ago, Congress created the Risk Mitigation Programs known as REMS to help FDA and manufacturers manage the risk of drugs. The current user fee agreement directs resources toward insuring the effectiveness of these important programs.

The new Generic Drug User Fee Agreement also contains important safety provisions, and this landmark measure will enable FDA to inspect overseas generic drug plants more often. As Pew's Drug Safety Project has noted, 80 percent of the ingredients in our drug supply now comes from outside the United States, yet FDA domestic inspections occur nearly every 2 years. And by way of contrast, inspections in China by the FDA occur, on average, every 17 years. Addressing this disparity will help protect patients from substandard drugs and even the playing field for U.S. manufacturers.

GDUFA is an important step forward for safety, and PDUFA funds will help evaluate drug safety. Medical devices are different. In contrast with drugs, medical devices can come to market with limited or no clinical data, and that makes it especially important that we have a robust postmarket surveillance system. And we urge Congress to allow FDA to apply user fees to device safety ini-

tiatives, something not covered to a great extent under the proposed agreement.

For example, PDUFA fees already support Sentinel for drug adverse events. PDUFA fees should be used to support the monitoring of devices in this program.

In closing, I would like to mention some of the other crucial activities that user fees do not cover such as ongoing inspections for brand name drugs, for example, and regulation of food safety. As important as user fees are, they are not a substitute for adequate appropriated funding.

The user fees, if they expire, would harm patients, public health, and the industry. We urge Congress to move quickly to pass these important bills and to ensure that FDA has continued sustained funding for its vital public health mission.

Thank you, and I would welcome any questions.

[The prepared statement of Mr. Coukell follows:]

PREPARED STATEMENT OF ALLAN COUKELL, B.SC.PHARM.

Based on data, science, and non-partisan research, the Pew Health Group works to reduce risks to the health, safety, and well-being of American consumers. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and stimulate civic life.

The user fee agreements can promote innovation, and help to ensure the safety and effectiveness of medical products ultimately with the goal of improving health. These agreements fund critical activities of the Food and Drug Administration (FDA).

Since 1992, user fee agreements have given FDA significant and sustained resources that allow the agency to review new products quickly. Preliminary findings of a study Pew has funded show that FDA reviews new drugs faster than its counterparts in the European Union and Canada.

The fees FDA collects under MDUFA provide the agency with additional resources to review applications and add about 200 much-needed staff members to the agency's Center for Devices and Radiologic Health (CDRH). Under the proposed agreement, the total fees collected over the 5-year period to 2017 are expected to reach $595 million. This will help create a more efficient center that is sufficiently resourced to better protect consumer safety and facilitate the introduction of innovative devices.

Overall, the user fee programs have substantially sped up the review of new drug applications. Review times are important insofar as they speed patients' access to potentially important products. The user fee agreements make review times a performance metric. However, true innovation is not just about getting products to market faster; it is about developing products that are safer or more effective than existing drugs and devices. While more challenging to measure than review times, improving health is the ultimate goal of the FDA.

THE USER FEE AGREEMENTS GIVE FDA MORE RESOURCES TO ENSURE DRUG SAFETY

While user fees primarily support the review and approval of medical products, some funds are available to partially underwrite certain product safety activities. The Generic Drug User Fee agreement will enable FDA not only to review generic drug applications, but also to inspect overseas drug manufacturing facilities more regularly.

Given the broad support for these agreements from Democrats, Republicans, the business community, and consumers, we urge Congress to move quickly to pass these important bills to ensure that FDA has continued, sustained funding to carry out and expand its important public health mission.

Chairman Harkin, Ranking Member Enzi, and members of this committee, thank you for the opportunity to testify about the importance of the user fee agreement legislation to patients and public health.

Based on data, science, and non-partisan research, the Pew Health Group works to reduce risks to the health, safety, and well-being of American consumers. Pew

applies a rigorous, analytical approach to improve public policy, inform the public, and stimulate civic life.

Today, I would like to talk about how the user fee agreements can promote innovation, and help to ensure the safety and effectiveness of medical products ultimately with the goal of improving health. These agreements fund critical activities of the Food and Drug Administration (FDA), the Federal public health agency that regulates important, life-sustaining products, such as drugs, vaccines, medical devices, biologics, and food, as well as other products people use daily, including cosmetics, vitamins, and, most recently, tobacco.

THE USER FEE AGREEMENTS PROMOTE INNOVATION

Since 1992, user fee agreements have given FDA significant and sustained resources that allow the agency to review new products quickly. Preliminary findings of a study Pew has funded show that FDA reviews new drugs faster than its counterparts in the European Union and Canada.

The 1992 Prescription Drug User Fee Act also established an accelerated regulatory review process for drugs that offer major advances or provide treatment where no adequate therapy exists. FDA devotes extra time and resources to drugs with priority review status.

This issue is particularly important to Pew's Antibiotics and Innovation Project, which is working to promote the development of new antibiotics needed to treat people suffering from serious and life-threatening infections. Since 2000, FDA granted priority review to 4 of the 11 new antibiotics (linezolid, daptomycin, tigecycline and fidaxomicin) that it approved, quickly bringing much-needed treatments for pneumonia, serious skin infections, and *Clostridium difficile*-associated diarrhea to market.[1] According to the Centers for Disease Control and Prevention, *Clostridium difficile*, a bacterium that can cause life-threatening infections, sickened 339,000 hospital patients in 2009 and is responsible for 14,000 deaths per year.[2]

In 2002, Congress established a user fee program for medical devices. We are asking that Congress swiftly reauthorize this program as well.

The fees FDA collects under MDUFA provide the agency with additional resources to review applications and add about 200 much-needed staff members to the agency's Center for Devices and Radiologic Health (CDRH). Under the proposed agreement, the total fees collected over the 5-year period 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 need for additional resources to boost the agency's capacity is especially important at CDRH. An analysis commissioned by the Pew Health Group examined CDRH, 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 fiscal year 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.

Overall, the user fee programs have substantially sped up the review of new drug applications. In the decade after the first user fee agreement was passed, the median review time fell from 27.7 months to 13.8 months. Review times for drugs given priority status have also fallen by half. Indeed, a standard review today is as fast as a priority review a decade ago (13.9 months).[3]

Review times are important insofar as they speed patients' access to potentially important products. The user fee agreements make review times a performance metric. However, it is critical to remember that true innovation is not just about getting products to market faster; it is about developing products that are safer or more effective than existing drugs and devices. While more challenging to measure than review times, improving health is the ultimate goal of the FDA.

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[1] *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*.

[2] Vital Signs: Preventing *Clostridium difficile* Infections. MMRW. March 9, 2012/61(09);157–62. *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6109a3.htm?s_cid=mm6109a3_w*.

[3] *http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm#compare*.

THE USER FEE AGREEMENTS GIVE FDA MORE RESOURCES TO ENSURE DRUG SAFETY

While user fees primarily support the review and approval of medical products, some funds are available to partially underwrite certain product safety activities. Five years ago, Congress created the risk evaluation and mitigation programs, known as REMS, as a new tool to help FDA and manufacturers manage the risks of drugs. The current user fee agreement directs resources toward ensuring the effectiveness of these important programs.

The new generic drug user fee agreement also contains important safety provisions. This landmark measure will enable FDA not only to review generic drug applications, but also to inspect overseas drug manufacturing facilities more regularly. Eighty percent of the ingredients in our pharmaceuticals come from foreign suppliers.[4] Yet, while FDA inspects American manufacturers every 2 years, it lacks the resources to conduct effective inspections of facilities in places such as China and India. In fact, FDA inspects overseas facilities on average every 9 years.[5] Addressing this disparity will help protect patients from substandard drugs and will provide a level playing field for generic drug makers that manufacture their products and source their ingredients domestically.

While GDUFA is a very important step forward in increasing drug safety, and PDUFA funds will help evaluate certain drug safety initiatives, we are disappointed that the draft MDUFA agreement does not allow FDA to apply user fees to fund some important medical device post-marketing surveillance activities. A robust post-market surveillance infrastructure is critical to ensure the safety of these products once they are on the market. Without adequate monitoring, it is difficult to identify devices on the marketplace with unexpected safety issues, which presents a threat to patient health. The user fee agreement should recognize that creating an effective post-marketing surveillance system is crucial to the willingness of the public and regulators to see devices come to market quickly, with less clinical data.

As a result, we urge Congress to allow FDA to apply user fees to certain device safety initiatives. PDUFA already provides funding for the agency's Sentinel Initiative, a proactive system for tracking drug adverse events. We believe this program should be expanded to include medical devices as well.

In closing, I would like to emphasize that as important as user fees are to the efficient function of FDA, they cannot be a substitute for adequate appropriated funding. User fees are not available for critical activities such as enforcing good manufacturing practices, most post-market safety activities, and for regulating non-drug products, such as food, which are not covered by user fee agreements. Furthermore, FDA is a public health agency that works to promote the health of all Americans. Because of the public interest in a well-performing FDA, the agency should receive public funds and be accountable to the public, not just to the industries it regulates.

If the user fee agreements expire, patients, public health, and industry will suffer. Given the broad support for these agreements from Democrats, Republicans, the business community, and consumers, we urge Congress to move quickly to pass these important bills to ensure that FDA has continued, sustained funding to carry out and expand its important public health mission.

Thank you and I look forward to answering any questions.

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

To all of you, again, thanks for your testimony. I will just take a few minutes here. I know time is progressing, but this is must-do legislation. We are going to have to get this done.

Around here, when there is legislation that must get through, things start coming out of the woodwork as we say. People have to hang something on it. They have something vitally important, you know, that has got to be done, and since there is no other, we will try to hang it on this. I have already seen some of that happening when people know that this bill must pass and has good bipartisan support.

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[4] U.S. Government Accountability Office (March 1998). Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program (Publication No. GAO/HEHS–98–21).

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

I have heard from all of you and from FDA what would happen if we did not pass it in time. But what I want to know is, will your organization, each of you, I ask this of all of you, will your organization help ensure that controversial policy measures do not derail the user fee reauthorization package? Sometimes we, here, need to count on all of you out there to make sure that we keep this intact and we keep controversial measures off of this.

Will your organization help ensure that that does not happen? Dr. Wheadon.

Dr. WHEADON. Certainly, Chairman Harkin. We completely agree with you. In fact, our original goal was a skinny PDUFA. We moved to a lean PDUFA. We now recognize we have a PDUFA that probably needs to go to Weight Watchers, but that having been said, we stand ready to work to ensure that those additions are kept to a minimum. And we will do our best to quickly facilitate any additions so that you can meet your timetable.

The CHAIRMAN. Appreciate that.

Miss Radcliffe.

Ms. RADCLIFFE. BIO has been very committed to making sure that controversial policy matters do not derail the PDUFA reauthorization.

As has been mentioned here earlier this morning, it is absolutely critical that PDUFA be reauthorized and well in advance of its expiration in September 2012 to avoid a reduction in force at the FDA. And even more, as I think was mentioned this morning, even the threat of a reduction in force at the FDA is extremely problematic for the agency, therefore for our sponsors, and therefore for patients.

So, yes, we remain very much in agreement with you.

The CHAIRMAN. Thank you.

Mr. Gaugh.

Mr. GAUGH. To answer your question, yes.

The CHAIRMAN. Dr. Nexon.

Mr. NEXON. Ditto.

The CHAIRMAN. Ditto.

Mr. COUKELL. Mr. Chairman, thank you.

I would like to thank you, the Ranking Member, and the members of the committee for moving quickly to reauthorize these important agreements. But also for the sustained bipartisan work that has gone into three additional discussion drafts that have been released or will be shortly on the drug supply chain, on incentivizing new antibiotics, and on medical device safety and innovation.

I think a lot of work has gone into hashing those out and making sure they are not controversial, and it is our hope that those will move with the reauthorization.

The CHAIRMAN. I appreciate all of that because this being a campaign year and a lot of campaigns out there from the top down, that I am concerned that things might try to interfere with the passage of this legislation, not for substantive reasons, but for political reasons.

That is why we need the industry out there, all of you who have a stake in this, who have been involved in the drafting and the putting of this together, and recognizing how necessary it is that

we pass it. That you will make sure that we have a bill that has broad consensus and that we do not get involved in controversial measures.

Senator Bennet.

Senator BENNET. Thank you, everybody, for all the work that you have done and for your testimony today.

I hope, what I am about to raise, is not a controversial measure. It is a complicated measure at the least, and a little bit of a freighted questions, but I think it is an important question to have, particularly in the context of all the agreement that has been reached here.

As all of you know, we have seen countless tragedies happen, tainted Heparin that made its way to patients killing over 100 Americans. Heat-sensitive insulin that was stolen and then redistributed to patients, millions of children's medicine pills recalled and taken off the shelves, counterfeit Avastin given to patients in need of chemotherapy, these issues really do demand Congress's attention. Everybody has been talking about having a uniform distribution system to increase the safety of drug distribution chain for years; some of you have talked about it for decades.

I believe that we can address the concerns and needs of the regulated community, address concerns raised by pharmacists about costs and provide the FDA with authority it says it needs to implement a system effectively to protect the public health. All of these are legitimate concerns that need to be reflected.

Pew has said before that they would like to see more effort applied to authenticating these products so people know what they believe they are taking corresponds to the actual products they ingest. Right now, we can learn more from a barcode on a gallon of milk than on a bottle of pills, pills that could be the difference between life and death. And that just does not seem right to people in Colorado, and I know other members of the committee feel the same.

This is not an easy issue. Everybody has different and legitimate concerns here whether it is the cost of implementation, or whether it is really a meaningful system that benefits the public health.

So my only question, this is the only one I am going to ask, is whether there is an interest in trying to work together to see if we can bridge this gap and create the kind of tracking system we need, so our constituents can have confidence in what they are ingesting.

That is for the whole panel or anybody that would like to talk about it.

Dr. WHEADON. Certainly, Senator Bennet. Our industry has stood ready and continues to stand ready to work with yourself, your staff, and the many other members that are very focused appropriately on this issue.

In terms of a system such as track and trace or a barcode, it is important that whatever that system may be it is uniformly adopted. It involves a number of other entities beyond simply drug manufacturers, pharmacies, distribution system, what have you. But that system needs to be uniform and applicable across the entirety of the system.

Ms. RADCLIFFE. I would echo what Dr. Wheadon has said. It is an issue that has been very important to BIO and its members, and we have worked hard with the stakeholder community to try and identify proposals that we all can stand behind.

I think we have made a tremendous amount of progress and we certainly look forward to working on that more where there are still some areas of disagreement, because the patchwork quilt of requirements does not serve patients well, and it is difficult for our members to comply with. So we do think that that needs to be addressed.

Mr. GAUGH. Yes, to answer your question, GPhA does support an alliance. And, in fact, is working with the PDSA, or the Pharmaceutical Distribution Security Alliance, across multiple stakeholders, and many of the stakeholders that you mentioned to create a system through a serialization process. As you said, bar coding on milk is known better and gives more information than it does, in some cases, on the pharmaceuticals.

So the PDSA group is working on a nationwide process, not a State by State, but nationwide that would help resolve that and we do support it.

Senator BENNET. Doctor, I will give you a pass unless you want to. No.

Mr. COUKELL. Senator, thank you for your leadership on this issue, and for your work with the Chairman and the Ranking Member.

I think consumers are surprised when they learn that we do not now have a system that routinely checks to see if the drugs they are about to get are counterfeit. Nor do we have a system that is able to track the product as it moves through the system, and a robust national system would be far preferable to a patchwork of State laws.

Senator BENNET. Thank you.

The CHAIRMAN. I just want to say to my friend from Colorado that I do not consider that controversial at all. We do need a good tracking system all the way from the manufacturers overseas, as we have said, with better inspections of those, and a trace and track system that comes all the way down. I do not consider that controversial.

I think most of the people here have said, and I agree with them, that we need a national system so that we do not have some hodgepodge of one State here, and one State there, and one State doing this. We need a national system of tracking.

Senator BENNET. I appreciate that, Mr. Chairman. And I think if we have the chance here, because of the good work that is going on, to try to get through this so that we do not go another decade, and another decade after that.

The CHAIRMAN. Absolutely.

Senator BENNET. I think that would be really welcome.

The CHAIRMAN. I look forward to working with you on that.

Senator BENNET. Thank you, Mr. Chairman.

The CHAIRMAN. Thanks.

Senator Blumenthal.

Senator BLUMENTHAL. Thank you, Mr. Chairman.

I want to thank you and our Ranking Member, but particularly you for your leadership in this whole area. A difficult and certainly challenging one, particularly in this political climate.

Mr. Coukell, if you could comment on one specific area that you have mentioned, the development of new antibiotics, why it is so critical, and why it should be part of this bill. As you know, Senator Corker and I have introduced a separate measure, which is largely incorporated in this bill, and your organization has been absolutely instrumental and enormously helpful and constructive in this effort.

I thank you and I invite you to comment on the need for this measure.

Mr. COUKELL. Thank you, Senator. And thank you and Senator Corker for your work on the GAIN Act, which you referenced.

As you know well, antibiotics are unlike other drugs in a couple of ways. A drug for high blood pressure will always be as effective as it is today, but antibiotics will lose effectiveness over time because the bugs will develop resistance.

Dr. Woodcock, this morning, talked about the declining pipeline for new drugs. That is especially acute in antibiotics, and we have more and more resistant infections emerging, and they tend to be small market drugs. We absolutely agree with you that we need incentives to make this an attractive play for companies to invest, so that we have a continued flow of new antibiotics.

Senator BLUMENTHAL. Thank you.

I want to ask a question for any member of the panel who wants to comment on what you think can and should be done to address the problem of drug shortages in this country. You probably heard some of my comments earlier, and I could expand on them now, but I think you got the drift of what my thinking is, and invite you to comment.

Mr. GAUGH. From the GPhA perspective, we have been working with the FDA on the drug shortage situation from a company, and an FDA. As I said in my testimony, the FDA and the generic industry has never been more collaborative than they are today.

We are, at GPhA, working on a system called Accelerated Recovery Initiative, ARI. In fact, we have a meeting with the FDA next week to discuss that model and how that can help resolve some of the drug shortage issues that are occurring today.

Senator BLUMENTHAL. How would that happen?

Mr. GAUGH. It would work with the FDA, with the manufacturers, through an independent third party, which would help, we hope, at an even earlier pace to identify a drug shortage that is occurring or about to occur. And then through the independent third party and the FDA working with the manufacturers separately to try to resolve the drug shortage as it is happening, to make it a less lengthy drug shortage, or maybe even to prevent it from happening.

Senator BLUMENTHAL. What about preventing it from happening? What can be done, for example, methotrexate, Doxil, or the anesthesiology medicines?

This problem really is one, as I do not need to tell anybody on the panel, or anybody in this room, of huge urgency and immediacy to anybody who goes to a hospital each day, anybody who talks to

a doctor who treats patients. This is very much on their minds, to say the least.

And I wonder whether the people in organizations like yours share this sense of urgency?

Mr. GAUGH. Our hope and belief would be that the ARI can be a more proactive solution to drug shortages. In today's environment, it is pretty much a reactive. When the drug company contacts the FDA, the FDA then goes into action to resolve the situation. So it is a reactive. As you said, methotrexate was one of those reactive situations.

So the ARI is our hope and our belief that working together with the FDA and through an independent third party, we can identify these at an earlier stage and help prevent them from even occurring.

Senator BLUMENTHAL. Before I conclude, anybody else on the panel have any comments on this issue?

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Blumenthal.

Again, I thank all the panel for being here, and I thank Dr. Woodcock and Dr. Shuren for remaining here for the duration of this.

I request the record be kept open for 10 days for other questions or submissions.

Again, I look forward to working with all of you to get this legislation through in a timely manner this year.

With that, the committee will stand adjourned.

[Additional Material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF SENATOR ROBERT P. CASEY, JR.

Thank you to the panelists for your remarks today. I'd also like to thank Chairman Harkin and Ranking Member Enzi for your leadership in guiding this committee toward several substantial and thoughtful bipartisan agreements on a variety of issues of critical import to American patients. I am glad to have had the opportunity to help to shape several of the agreements, and I look forward to working with you to ensure they are included in the upcoming Food and Drug Administration (FDA) Reauthorization package to be considered by this committee.

I am proud to come from a State with a strong history of leadership in medical discovery. During the past year, I have been meeting with and working with many Pennsylvanians to bring forward and support new proposals that will enhance rewards for biomedical research and strengthen FDA's ability to protect patient safety and at the same time improve access to medical breakthroughs. I was glad to have played a role in helping to advance bipartisan agreements in the HELP Committee to modernize and strengthen the FDA's ability to respond, and pro-actively address, significant public health threats such as the unprecedented growth in prescription drug shortages, the surge of antibiotic-resistant "super bugs," and gaps in the current FDA approval pathway with respect to novel low-to-moderate risk medical devices.

Guaranteeing the safety and effectiveness of medical products is a task of paramount importance to the American public. It is also a responsibility that carries with it the need to work diligently with critical health care industries, such as pharmaceutical companies and medical device makers, to drive progress in biomedical medicine and regulatory science and help shepherd significant new cures and treatments to patients with unmet medical needs.

Currently, the growing manufacturing, sourcing and rapid dispersion of medical products from outside the United States to the medicine cabinets and hospital beds of American patients is a cause of great concern. Federal laws regulating such activity have not been updated in decades and FDA is left relying upon statutes from a time when the vast majority of medicines were discovered, developed and distributed within the United States. We cannot allow this to continue as the status quo. Recent cases such as the counterfeit of Avastin and Heparin showcase the life-threatening failings of our current system.

It is crucial that, during this reauthorization, we update our regulatory oversight and infrastructure at the FDA, and give the FDA the appropriate authority and resources, so that it can ensure that all products that reach American patients—regardless of where they are made, or who distributes them—are safe and effective. That is the public's expectation, and that should serve as our North Star. In addition, I think that we must not lose focus on the fact that, at the end of the day, patients are depending on the FDA to not just review and approve new products, but help to facilitate progress in science and medicine that will lead to life-saving discoveries.

Historically, the FDA has done an outstanding job in achieving all of these goals, but there is more work that remains to be done. The onus rests on Congress to help provide FDA with the guidance and wherewithal to meet the needs of an increasingly diverse and aging population, and overcome the unique challenges presented by our 21st century global economy.

Chairman Harkin and Ranking Member Enzi, I look forward to working with you, and others on this committee, towards these shared goals.

[Whereupon, at 12:24 p.m., the hearing was adjourned.]

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