

FDA USER FEE AGREEMENTS: IMPROVING MEDICAL PRODUCT REGULATION AND INNOVATION FOR PATIENTS, PART I

HEARING

OF THE

**COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS**

UNITED STATES SENATE

ONE HUNDRED FIFTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING FDA USER FEE AGREEMENTS, FOCUSING ON IMPROVING
MEDICAL PRODUCT REGULATION AND INNOVATION FOR PATIENTS,
PART I

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MARCH 21, 2017
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C O N T E N T S

STATEMENTS

TUESDAY, MARCH 21, 2017

Page

COMMITTEE MEMBERS

| | |
|--|----|
| Alexander, Hon. Lamar, Chairman, Committee on Health, Education, Labor, and Pensions, opening statement | 1 |
| Murray, Hon. Patty, a U.S. Senator from the State of Washington, opening statement | 4 |
| Burr, Hon. Richard, a U.S. Senator from the State of North Carolina | 45 |
| Collins, Hon. Susan M., a U.S. Senator from the State of Maine | 49 |
| Bennet, Hon. Michael F., a U.S. Senator from the State of Colorado | 51 |
| Young, Hon. Todd, a U.S. Senator from the State of Indiana | 53 |
| Murphy, Hon. Christopher, a U.S. Senator from the State of Connecticut | 54 |
| Roberts, Hon. Pat, a U.S. Senator from the State of Kansas | 56 |
| Warren, Hon. Elizabeth, a U.S. Senator from the State of Massachusetts | 57 |
| Hassan, Hon. Maggie, a U.S. Senator from the State of New Hampshire | 61 |
| Cassidy, Hon. Bill, a U.S. Senator from the State of Louisiana | 63 |
| Whitehouse, Hon. Sheldon, a U.S. Senator from the State of Rhode Island | 64 |
| Scott, Hon. Tim, a U.S. Senator from the State of South Carolina | 66 |
| Kaine, Hon. Tim, a U.S. Senator from the State of Virginia | 68 |
| Franken, Hon. Al, a U.S. Senator from the State of Minnesota | 71 |

WITNESSES

| | |
|--|----|
| Woodcock, Janet, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD | 6 |
| Prepared statement | 8 |
| Marks, Peter, M.D., Ph.D., Director, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD | 42 |
| Shuren, Jeffrey E., M.D., J.D., Director, Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD | 44 |

**FDA USER FEE AGREEMENTS: IMPROVING
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TUESDAY, MARCH 21, 2017

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

The committee met, pursuant to notice, at 10:05 a.m. in room SD-430, Dirksen Senate Office Building, Hon. Lamar Alexander, chairman of the committee, presiding.

Present: Senators Alexander, Burr, Collins, Cassidy, Young, Roberts, Scott, Murray, Franken, Bennet, Whitehouse, Murphy, Warren, Kaine, and Hassan.

OPENING STATEMENT OF SENATOR ALEXANDER

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

We are holding a hearing today on Food and Drug Administration User Fee Agreements: Improving Medical Product Regulation and Innovation for Patients, Part I.

Senator Murray and I will each have an opening statement and then we will introduce our panel of witnesses. After our witness testimony, Senators will have 5 minutes of questions.

The subject today is the Food and Drug Administration's Medical Device and Drug User Fees. It seems like a long time ago—but it really was not very long ago—that Congress passed the 21st Century Cures Act. Ninety-four Senators voted for it. President Obama and Vice President Biden were strongly in support of it, so was Speaker Ryan. Mitch McConnell called it the most important piece of legislation in the last Congress.

That came through this committee, and I thank the members of the committee, especially, for resolving our differences of opinions and making it possible for us to reach consensus.

That bill was about moving medical products, drugs, and devices more rapidly in a safe way through the investment and the regulatory process, and into the hands of patients and doctors' offices.

Today, we are talking about really implementing that great goal, one that shows so much promise for virtually every American. We are here to talk about how we continue to fund the Food and Drug Administration, which is the agency responsible for making sure the promising research supported by the 21st Century Cures Act actually reaches patients.

We will hear from witnesses from the agency itself to tell us how the User Fee Agreements will improve the agency's abilities to regulate medical products and promote innovation.

We will hear from patients, device manufacturers, and brand and generic drug manufacturers in a second hearing, which is tentatively scheduled for April 4.

I want to thank the witnesses for taking the time to testify today. We respect the great amount of expertise and service that you have given to our country. I want to thank you, also, for moving so quickly to implement the 21st Century Act. I noticed especially that the provision involving regenerative medicine was published within about a month after President Obama signed the law.

The first medical product User Fee Agreement was enacted in 1992. The FDA worked with the drug manufacturers to hammer out an agreement that the agency would collect user fees from drug manufacturers in exchange for more timely, predictable reviews. The agreement was a success. It decreased review times and increased patient access to medicines.

Before September 30 of this year, four different User Fee Agreements need to be reauthorized. The Prescription Drug User Fee is the first one. It is common around here to call it PDUFA. I am not going to do that. I just cannot stand PDUFA, and MDUFA, and GDUFA, and the other UFA.

[Laughter.]

I am going to call them, if you do not mind, the Prescription Drug User Fee, which accounted for over 70 percent of the brand drug review in 2015.

The second one is the Medical Device User Fee, which accounted for 35 percent of the medical device review budget in 2015.

The Generic Drug User Fee accounted for 70 percent of generic drug review budget.

The Biosimilar User Fee accounted for 7 percent of the biosimilar review budget.

A lot of the money for the FDA comes from these agreements with manufacturers of prescription drugs and devices.

The authority for the FDA to collect user fees for medical product review will expire on September 30 of this year, 6 months from now.

This is probably the most important part of what I have to say this morning.

If we do not move quickly to authorize these Agreements, the FDA will be forced to begin sending layoff notices to more than 5,000 employees to notify them they may lose their jobs in 60 days. That is what they have to do by law.

A delay in reauthorizing these Agreements would delay the review of drugs and devices submitted after April 1, only a few days away.

For example, if we do not pass these reauthorizations into law before the current Agreements expire, an FDA reviewer, who gets started reviewing a cancer drug submitted to the agency in April, would be laid off on October 1 before the reviewer is able to finish his or her work.

The sooner we reauthorize the Agreements, the better, to give patients, reviewers, and companies certainty.

In addition to harming patients and families that rely on medical innovation, a delay in reauthorizing the User Fees would threaten biomedical industry jobs and America's global leadership in biomedical innovation.

I am hopeful that this committee, and this Congress, can work in a bipartisan manner to reauthorize the User Fees before the August recess. Congress must pass legislation reauthorizing and updating the fees to support the recommendations contained in what are called "commitment letters" sent to Congress in January.

These commitment letters are part of the Agreements between the FDA and the industry to establish the agency's commitments, such as timelines for application review or to put out guidances in exchange for the fees that Congress authorizes.

The letters were transmitted to Congress in January of this year. Today's hearing is not the first time Members of Congress, or the public, is hearing about the recommendations for reauthorization.

In Congress, while we were working on the 21st Century Cures, after it was signed into law, the HELP committee had 15 bipartisan hearings throughout that time—before it was signed into law and after it was signed into law, the 21st Century Cures some of which were in conjunction with the Energy and Commerce Committee in the House of Representatives—so that we could hear from the FDA and industry about the reauthorization. The first of those briefings was back in late 2015.

Outside of Congress, the FDA posted meeting minutes after every negotiation and held public meetings to hear feedback. The content of the commitment letters and the changes to the fee authorizations should not be new or a surprise for any member of this committee.

After the April 4 hearing, I hope to move to markup the legislation in committee as soon as possible. This is the first time the User Fees have sunset in the first year of a new administration, so we are starting hearings a little later this year than we did in 2012.

In order to get this done on time, any additional policies that Senators may want to attach need to be broadly bipartisan, related to human medical products, and noncontroversial in order to avoid slowing the package down.

There are many improvements in the commitment letters and fee structures in these reauthorizations to be excited about.

The Prescription Drug and Medical Device reauthorizations included many provisions that build on the work of 21st Century Cures such as involving patients in the drug and medical device development. A dedicated staff to assist in the development and review of rare disease drugs, improved timelines, increased guidance for drug and device combination products, and modernizing the clinical trial process.

There are structural reforms. Each Agreement contains reporting measures built both by the FDA and by independent third parties so we can see how the changes are working.

The FDA is going to work to implement full-time reporting by 2022, so Congress, patients, and medical product manufacturers will have a better picture about how resources are being used at the FDA and understand what is needed to do what we ask.

The Biosimilar and Generic Drug User Fees Agreement includes additional staff and resources to approve more biosimilars and more generic drugs, which provide more competition and lower drug costs.

These are just a few of the highlights of the reauthorization and commitment letters. It is a good Agreement for patients, and I look forward to working with Senator Murray and all the members of the committee to get it done expeditiously.

Senator MURRAY.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Chairman Alexander.

Thank you to all of our colleagues and our witnesses for joining us today.

Mr. Chairman, before I start, I want to talk about the letter that every Democrat on this committee signed and sent to you this past Friday requesting that our hearing on User Fees be delayed in order to make time for an urgently needed discussion of Trump Care.

To be frank, the hearing that we are having today seems inappropriate for the moment that we are in. House Republicans' Trump Care bill could be on the House floor in a matter of several days.

This is legislation that will take tens of millions of people off of coverage, cause premiums to spike, target seniors with higher healthcare costs just because of their age, end Medicaid as we know it, and make coverage too expensive for millions of rural and older Americans, and cutoff access to critical health services at Planned Parenthood. And I could go on.

Trump Care will cause all this harm and more, while giving the wealthiest one-tenth of 1 percent of Americans a nearly \$200,000 tax cut, and give insurance company executives a massive tax break as well.

Senator McConnell has indicated that Trump Care could change significantly in the Senate if it passes the House. But instead of giving Senators time to review and evaluate a possibly very different bill, he has indicated it will go straight to the floor for a vote.

We are talking about legislation that will have a profound and profoundly negative impact on the lives, well-being, and financial security of people across the country. People who, I might add, are truly terrified about the uncertain path forward.

The idea that our committee, the Health Committee, would not have a single hearing to discuss and debate it is completely appalling, and leaves me very concerned that our bipartisan tradition on the HELP Committee is continuing to give way to extraordinary partisanship from Republican leaders in the Trump administration.

I really hope that we see a reversal of this pattern, and I hope it begins with a HELP Committee hearing on the impact of this legislation, especially given that I know Democrats are not the only ones with grave concerns about the many ways that Trump Care could hurt women, and families, and seniors nationwide.

I hope the Republicans do the right thing, step back from the precipice, and work with us to strengthen our healthcare system,

not destroy it. It would be truly unfortunate if this intense partisanship from Republicans in the healthcare arena were to impact Congress' ability to work together on shared priorities, like reauthorizing the User Fee Agreements this year.

The already finalized User Fee Agreements for drugs, generics, biosimilars, and medical devices reflect thorough negotiations. They will help support the growth and maturation of the FDA to an agency ready for 21st century technology and the movements toward precision medicine, and build on the bipartisan policies passed in the 21st Century Cures Act last year.

Especially in light of a very tight fiscal reality, these Agreements are an important tool to help make sure that the FDA can uphold its gold standard of approval while evaluating new drugs and devices efficiently.

I oppose efforts by the Trump administration to take unprecedented actions to alter these Agreements or to undermine the important public health work of the agency. I am also concerned that the Administration is hampering the FDA by depriving it of key staff, blocking it of key staff, and blocking its ability to issue the guidance and regulations needed to foster innovation.

Moving forward with the Agreements as already finalized is absolutely necessary if Congress wants to advance safe, effective, and innovative medical products for patients and families across the country. Without these Agreements, the agency will be crippled.

Another key concern for me—and one that I know is a huge burden for families in my State and nationwide—is the astronomically high price of prescription drugs. To be clear, the FDA's approval processes and standards are not direct causes of high drug prices. But everyone in this room knows we are facing a dire situation when it comes to the rising costs of drugs.

Our broken system results in patients and families across the country being unable to afford the drugs and treatments they need. And this is a situation that does demand action from this committee.

I know our Members on both sides of the aisle have ideas about ways to reduce the burden of drug costs and I am committed to working with all colleagues on both sides of the aisle on this issue.

Chairman Alexander, I do want to reiterate my sincere disappointment and really shock that there is so much at stake for patients and families in the bill working its way through the House now and here, apparently, to the Senate very quickly. That that kind of bill could be jammed through the Senate in a matter of days and this committee having no formal opportunity to discuss it is really concerning.

We all should know, Trump Care is causing millions of people fear and worry, and while there is every reason for Republicans to want to avoid talking about its disastrous consequences, that is no excuse for trying to make it an elephant in the room.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray.

We have this opportunity to talk about the Food and Drug Administration User Fees. We have the experts from the agency here to do that today and April 4, tentatively scheduled, we will have

patient safety groups and manufacturers here to talk. So I hope we can take full advantage of the time.

We have a vote scheduled for noon. I will be glad to come back if Senators have more questions of the FDA representatives or something they would like to say.

Each witness will have up to 5 minutes to give his or her testimony. I am pleased to welcome our three witnesses to today's hearing.

First, thank you for taking time to be here.

The first witness is Dr. Janet Woodcock. We know her well. She is Director of the Center for Drug Evaluation and Research at the FDA, which performs the critical task of ensuring safe and effective drugs are available to improve the health of people in the United States.

She has been at the FDA for 30 years, and been the Center Director since Congress reauthorized the Prescription Drug User Fee Agreements and first authorized the Biosimilar and Generic Drug Agreements in 2012.

We will then hear from Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research at the FDA. He joined the Center as Deputy Center Director in 2012 and became Center Director in 2016. The Center for Biologics Evaluation and Research is responsible for ensuring the safety and effectiveness of biological products including vaccines, and cellular and gene therapies.

I look forward to hearing how the User Fee funds will help the Center keep up with rapidly advancing science and promote certainty for sponsors.

Third to testify will be Dr. Jeffrey Shuren. He is Director of the Center for Devices and Radiological Health, which is responsible for ensuring the safety, effectiveness, and quality of medical devices and fostering device innovation. He has been Director since January 2010.

Welcome, again, to this panel of experts.

Dr. Woodcock, we will start with you.

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, members of the committee.

I am glad to be here to discuss three Drug User Fee programs that are due for reauthorization in fiscal year 2018.

The first one, the Prescription Drug User Fee Act program supports innovation. That is basically what that one is about. PDUFA has resulted in fast and predictable review of innovative therapies for Americans.

U.S. patients are first in the world to get innovative therapies in over two-thirds of the cases. Compared to the entire rest of the world, they are first.

New therapies often are for rare, fatal, untreatable diseases, orphan conditions, cancers, degenerative neurologic diseases. These are important therapies that the PDUFA program helps get to the market in many cases.

In some cases recently, with the advance of science, we have actually been able to get cures onto the market. For example, the hepatitis C drugs are curing that infection, that chronic infection that was resulting in so many transplants in chronically ill people.

Programmatic improvements that are envisioned in the next PDUFA program include more support for a breakthrough therapy program. This was enacted by Congress around 5 years ago, and has been extremely successful in getting those breakthrough game-changing drugs to patients in as quick a manner as possible. This Agreement would provide more support for that program.

Advancing the use of surrogate endpoints; surrogate endpoints are used to speed market access when the actual clinical outcomes might take a very long time.

Accelerating drug development tools; this is something that this committee paid a great deal of attention to in the 21st Century Cures, the biomarkers, and so forth. The new PDUFA agreement would provide additional support for that as well as complex trial designs.

Also, there is additional support in renovation for our review of combination products. These are becoming more and more common. We have auto-injectors. We have drugs and devices that are used together in different ways, and we need to make sure those reviews are predictable, that they are streamlined, and we can get those innovative products to patients as soon as possible.

And finally, there are provisions for supporting our evaluation of real world evidence; another type of evidence that was discussed in the Cures legislation.

The second User Fee program is the Generic Drug User Fee program. This would be the second version of this program. GDUFA, instead of supporting innovation, it supports affordability of drugs by introducing generic competition. Almost 90 percent of prescriptions that are dispensed in the United States today are generic drugs. This program over the years has been extremely successful.

It is estimated that over a decade, it has saved U.S. consumers about \$1.5 trillion by being able to purchase affordable generics instead of expensive brand drugs.

The first Generic Drug User Fee program had quite a few problems because there was a huge backlog. The success of the program had really overwhelmed our ability to review all these generic drugs. But we also had a non-automated paper-based review process, and thousands and thousands of generic drugs to review.

GDUFA I, met or exceeded all its submission review goals. All those thousands of drugs have been taken up into the review process and are in process or on the market. In fact, about one-quarter of all currently approved generic drugs have been approved in the last 4 years.

We approved in 2016 alone, the highest number of generic drugs ever approved in a year; 835 generics approved or tentatively approved. Of all of those generics we approved, 405 of those during the program were first generics, so the first competitor to come onto the market for a brand drug; a very important landmark.

GDUFA II, the second program, builds on the first. It provides for a faster review of priority applications. Those would be applica-

tions that lack that competition and they would be reviewed within 8 months.

There is also for the complex generics—those that are not simple tablets, but may have an auto-injector or a device associated with them, or they may be a very complicated molecule or dosage form—it provides for a preprogram where they can come in and talk to us. We can help them with their development. This is what we do for innovator drugs. There is also going to be more communication and improved facility assessments.

The third program is the Biosimilars User Fee Act, and this is again different. The Biosimilars Act, with the help of Congress and your legislation, is establishing a new industry, the biosimilars industry. It will provide competition for those biological drugs, most of which are very expensive.

We have already approved four biosimilar products, which provide competition to very widely used biologic drugs and there are numerous applications that we are reviewing in-house. There are actually 64 biosimilar products in development programs. So we hope to grow this program in the next User Fee program.

These have all benefited patients, the medical community, and the public.

I would really be happy to answer any questions you might have.

[The combined prepared statement of Dr. Woodcock, Dr. Marks and Dr. Shuren follows:]

PREPARED STATEMENT OF JANET WOODCOCK, M.D., PETER MARKS, M.D.,
AND JEFFREY SHUREN, M.D., J.D.

INTRODUCTION

Mr. Chairman and members of the committee: We are the directors of the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) at the U.S. 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 reauthorization of the Prescription Drug User Fee Act (PDUFA VI), the reauthorization of the Medical Device User Fee Act (MDUFA IV), the first reauthorization of the Generic Drug User Fee Amendments (GDUFA II), and the first reauthorization of the Biosimilar User Fee Act (BsUFA II). The User Fee programs help FDA to fulfill its mission of protecting the public health, while improving the predictability of review processes and accelerating innovation in the industry. Since the inception of these programs, FDA has dramatically reduced the review time for new products, without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs or devices prior to approval.

The reauthorization proposals for PDUFA, MDUFA, GDUFA, and BSUFA that are described below were submitted to Congress in January, under the previous Administration and reflect a different approach to the Federal Budget. The Blueprint Budget supports many of the goals of the reauthorization proposals but proposes a different way of financing these goals. The Administration looks forward to working with Congress, with industry input, to develop reauthorization proposals that speed the development and approval of vital medical products that are safe and effective.

PDUFA

The timely review of the safety and effectiveness of new drug applications (NDAs) and biologics license applications (BLAs) is central to FDA's mission to protect and promote the public health—and PDUFA is essential to these efforts.

Before PDUFA's enactment in 1992, Americans' access to innovative, new medicines lagged behind other countries. FDA's pre-market review process was understaffed, unpredictable, and slow. The Agency lacked sufficient staff to perform timely reviews or develop procedures and standards to assure a more rigorous, consistent, and predictable process.

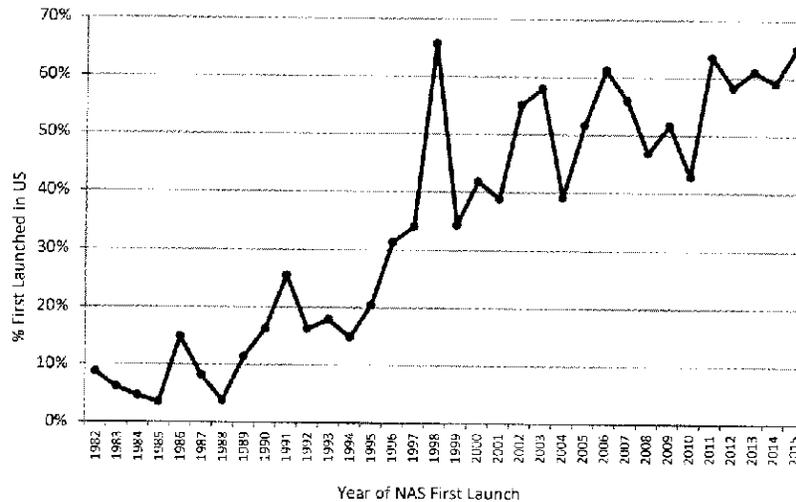
To tackle these challenges, Congress passed PDUFA, which authorized FDA to collect industry user fees to hire additional staff and upgrade its information technology systems. In return, it committed the Agency to speed the application review process for new drugs without compromising its high standards for new drug safety, efficacy, and quality.

Speeding Americans' Access to Safe and Effective New Therapies

PDUFA has revolutionized the United States' drug approval process. It reversed the lag in drug approvals that prompted its creation, providing Americans with more rapid access to safe and effective new drugs and biologics.

As shown in Figure 1, today, almost two-thirds of new active substances approved in the world market are launched first in the United States. To put this figure in perspective, that is more than triple the rate approved first in the United States in the first year of PDUFA.

**Figure 1. US Share of New Active Substances (NAS)
Launched on the World Market**



Source: *Scrip Magazine* (1982 - 2006), *Pharmaprojects/Citeline Pharma R&D Annual Review* (2007 - 2016)

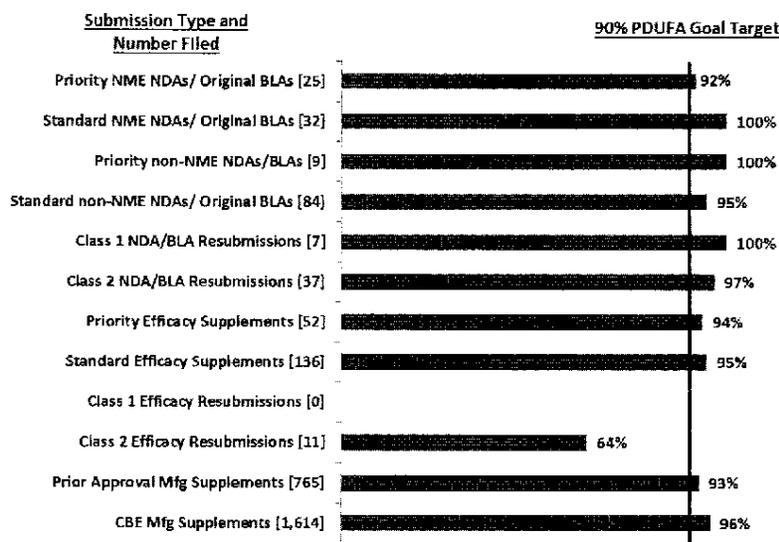
The 5-year reauthorization cycles for PDUFA have supported continuous program innovation, evaluation, and improvement. The enhancements to the process of human drug review originally focused on the FDA pre-market review of NDAs and BLAs. Through successive PDUFA reauthorizations, program enhancements have evolved and expanded to include extensive communication and consultation between drug sponsors and FDA throughout drug development. This has enabled better incorporation of advances in regulatory science applied to drug development and regulatory oversight. The continued modernization of drug review under PDUFA has also strengthened and enabled innovation in approaches to post-market safety. Most recently, the program has been enhanced by increasing patient focus and modernizing supporting informatics.

These enhancements have contributed to the United States becoming a global leader in drug innovation and Americans are typically the first to benefit from safe and effective new medicines. PDUFA, with its reauthorization cycles, has resulted in a scientifically and financially strong program with transparent stakeholder engagement as a routine way of doing business.

Throughout this program evolution, FDA has continued to review large volumes of sponsor submissions and deliver predictably high levels of performance against

PDUFA goal commitments for timely regulatory review and development phase consultation, as shown in Figure 2.

Figure 2. FDA Review Performance - FY 2015: Percent of Submissions Acted on by Goal Date¹

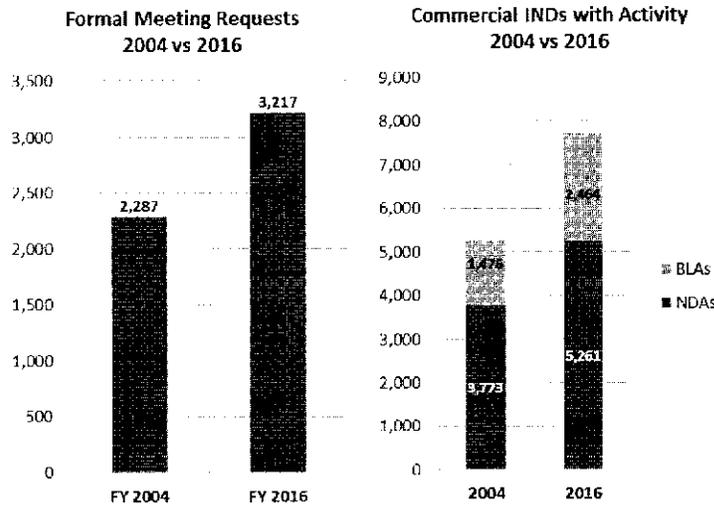


Increasing the Timeliness and Efficiency of Premarket Review

A key element of the success of the PDUFA program is ongoing development-phase consultation provided to drug sponsors by FDA, helping to minimize unnecessary or suboptimal development steps, and getting important new drugs to patients more rapidly and efficiently. FDA's capacity to provide sponsors, including small first-time innovators, with timely advice enabled by PDUFA funding, has contributed to the strong drug development pipeline in the United States today. This is reflected in the increased numbers of drug development programs underway in companies, and the corresponding growth in company requests for development phase meetings with FDA, as shown in Figure 3.

¹NME = New Molecular Entity; NDA = New Drug Application; BLA = Biologic Licensing Application; CBE = Changes-Being-Effectuated.

Figure 3. FDA Commercial Investigational New Drug (INDs) with Activity and Formal Meeting Requests 2004 vs. 2016

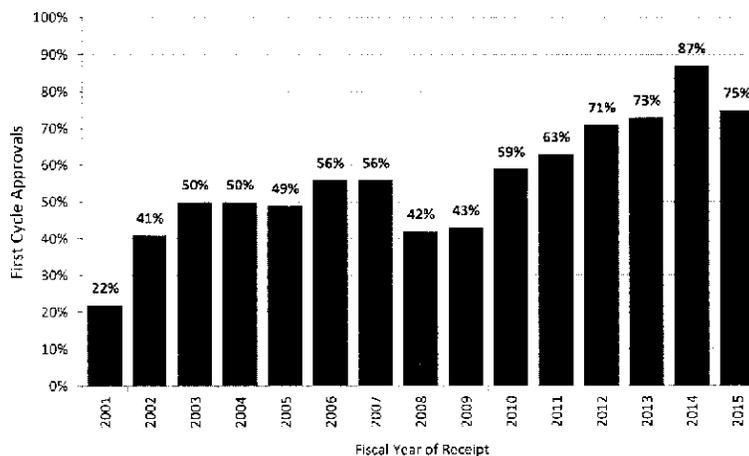


- IND Data represents a 12 month Academic period of July 1st-June 30th
- Activity is defined as any incoming submissions received within the reporting period on/after the date of the new IND application.
- Meeting Data as of 9/30/2016.
- Data includes activity for both FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

The volume of formal meetings requested by drug sponsors has steadily grown over the course of PDUFA. Early and frequent communication between sponsors and FDA serves to improve the efficiency of drug development. Indeed, it is one of the cornerstones of the Breakthrough Therapy program. FDA-sponsor meetings help sponsors navigate key milestones during drug development, support the assembly and submission of sponsors' marketing applications, and enable sponsors to clarify requirements for complete application submissions and potentially avoid the need for an additional review cycle.

The improvement in the quality of drug development programs and the submitted applications, supported by these PDUFA-enabled consultations between FDA and drug sponsors, is but one explanation for the observed trend toward higher first cycle approvals of applications for novel drugs (referred to as new molecular entity (NME) NDAs and BLAs), as shown in Figure 4.

**Figure 4. FDA NME NDA/BLA
First Action Approval Rate**



- Multiple applications pertaining to single new molecular/biologic entity (e.g. single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.
- Original BLAs that do not contain a new active ingredient are excluded. Percentages exclude pending applications from the denominator.
- Data includes activity for both FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

Development-phase consultations can be particularly helpful in support of the most innovative drug programs. Of the NME NDAs and BLAs that FDA approved in calendar year (CY) 2016, over one-third were indicated for rare diseases. In addition, over one-third (36 percent) of the drugs approved by the Center for Drug Evaluation and Research were first in their drug class and over 80 percent (86 percent) were approved first in the United States.

While a standard review is typically completed in 10 months, FDA expedites review for priority drugs to be completed within 6 months. Priority drugs are generally targeted at severe illnesses with few or no available therapeutic options. They typically receive greater assistance from FDA reviewers throughout the development process, including providing advice in the design and implementation of the clinical trials necessary to demonstrate product safety and effectiveness.

In 2016, over 60 percent of NME NDAs and new BLAs approved by FDA benefited from one or more of FDA's expedited programs.

Expanded Access to Investigational Products

While the best means of providing access to useful medical treatments for all Americans is to approve drugs demonstrated to be safe and effective as quickly as possible, FDA also recognizes circumstances in which there may be value to patients and physicians in having access to products prior to marketing approval. In some cases where an individual has a serious or life-threatening disease and lacks a satisfactory therapy, that individual may believe that a promising but not yet fully evaluated treatment is his or her best choice.

FDA allows for access to investigational products through clinical trials and the Agency's Expanded Access program. Clinical trials collect the necessary clinical information needed for FDA review and, if appropriate, approval, of investigational drugs, thereby making the drug widely available to patients. However, there are times when an individual cannot enroll in a clinical trial. In these cases, the patient may be able to gain access to an investigational therapy through the Expanded Access program.

In order for an individual patient to qualify for the Expanded Access program, several criteria must be met, including that the patient must have a serious or life-threatening disease or condition and no comparable or satisfactory alternative therapy. The patient's physician then approaches the pharmaceutical company to ask for its agreement that it will provide the drug being sought. The company has the right to approve or disapprove the physician's request. If the company agrees to the physi-

cian's request, the physician can then apply to FDA for authorization to proceed. Should they do so, they are highly likely to be allowed to proceed with the expanded access use. FDA has authorized more than 99 percent of the requests received in fiscal years 2010–15. Emergency requests are usually granted immediately over the phone and non-emergencies are processed in a median of 4 days.

Access to investigational products requires the active cooperation of the treating physician, industry and FDA in order to be successful. In particular, the company developing the investigational product must be willing to provide it—FDA cannot force a company to manufacture a product or to make a product available. Companies might have their own reasons to turn down requests for their investigational products, including their desire to maintain their clinical development program or simply because they have not produced enough of the product.

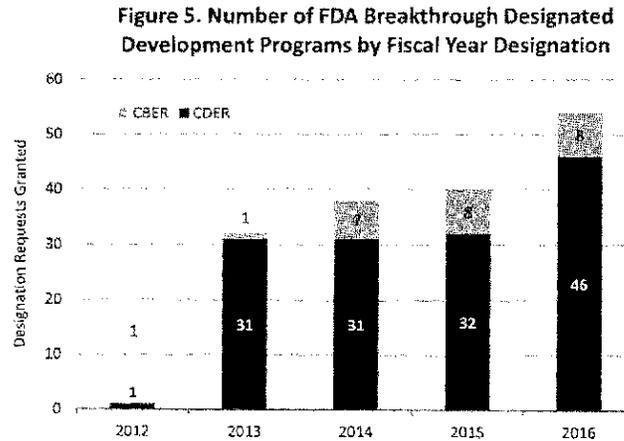
For over 20 years, FDA has been committed to ensuring that this program works well for patients and has recently made significant improvements to its functioning and efficiency.

Breakthrough Therapy Designation

The Breakthrough Therapy (BT) program, authorized by the FDA Safety and Innovation Act (FDASIA), has further enhanced the engagement of FDA and sponsors during drug development. This program, which is for new drugs to treat serious and life-threatening diseases with unmet medical need, calls for intensive FDA-sponsor consultation during development, when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.

Given the known benefits of development-phase consultation with FDA, the BT designation has been much sought after by sponsors. As of November 30, 2016, FDA had received 492 requests for BT designation and had granted 165 requests. Figure 5 shows the trend of increasing numbers of development programs.

Figure 5. Number of FDA Breakthrough Designated Development Programs by Fiscal Year of Designation



Although oncology, hematology and antiviral products account for the largest share of BT designation requests in CDER, it should be noted that BT requests and the granted designations and ongoing programs span the entire spectrum of disease areas as shown in Figure 6a, reflecting granted designations as of November 30, 2016. In CBER, most of the BT designation requests and granted designations are for gene therapies, vaccines and immunotherapies as shown in Figure 6b.

Figure 6a. CDER Breakthrough Therapy Requests Granted by Product Type

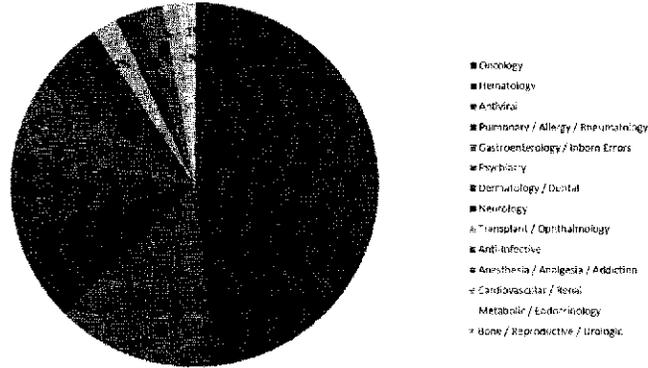
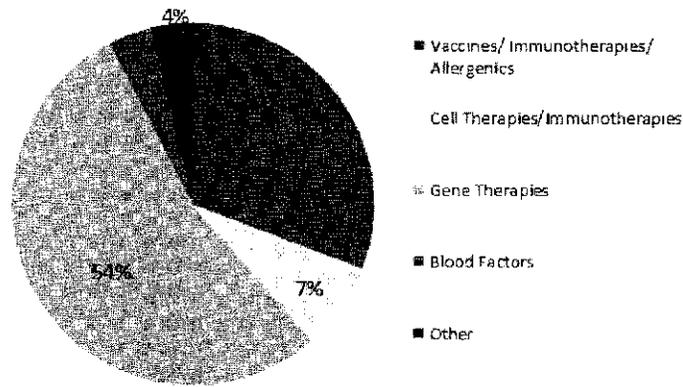


Figure 6b. CDER Breakthrough Therapy Requests Granted by Product Type



Data as of 12/1/16. Figures include total # of granted breakthrough designations for drug/indications under active IND development but have not yet received marketing approval or rescission decision.

PDUFA V

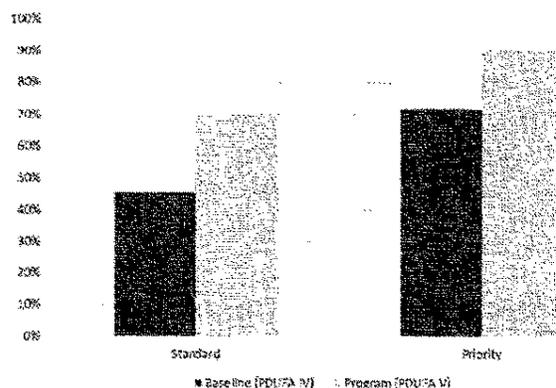
We are currently in the final year of the PDUFA V program. Over the years since the start of PDUFA I in 1992, the complexity of scientific and clinical issues in the study of new drugs has grown, including use of genetic targeting, biomarkers, novel trial designs, plans and programs to ensure effective post-market risk management. These approaches and issues were less common or nonexistent at the start of PDUFA. In addition, predictability and increased communication with FDA during drug development and application review emerged as a top priority for drug sponsors.

PDUFA V sought to achieve a better balance between the desire for increased communication with sponsors and the need to ensure adequate review time for the most complex and innovative products reviewed by FDA. This resulted in a cornerstone of the PDUFA V agreement, a new program for NME NDAs and BLA reviews that is designed to promote greater transparency and improve communication between the FDA review team and the applicant. We anticipated that the increased communications before application submissions and at key points within the first review cycle would ensure that FDA had access to all of the information that might inform and enable a first-cycle approval for those applications that could be approved, avoiding unnecessary additional cycles of review. This would enable faster

access to new drugs for the patients who need them and would help reduce avoidable costs for drug sponsors.

A key measure of program success is the percentage of applications approved in a single, first review cycle. Figure 7 illustrates the success of the PDUFA V NME Program in achieving its first cycle review goals for both standard and priority reviews. The figure presents the share of first-cycle approvals for priority and standard NDAs and BLAs filed. First cycle approvals for NME NDAs and new BLAs have been significantly higher under the new PDUFA V review program.

Figure 7. Findings of the Final Assessment of the PDUFA V NME Review Program



Data includes activity for both FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

Other PDUFA V enhancements include improved communications during drug development, strengthening the rare disease program, exploring new methods for regulatory science, and implementation of structured benefit-risk assessment. PDUFA V also provided for additional drug safety enhancements focused on standardizing the design of Risk Evaluation and Management Systems (REMS) and using the Sentinel Initiative, FDA's active surveillance systems for post-market safety (see PDUFA IV), to evaluate drug safety issues. This has prepared the way for expanded reliance on the data from Sentinel.

Patient-Focused Drug Development

As part of the PDUFA V benefit-risk assessment initiative, FDA and industry recognized that patients are uniquely positioned to inform aspects of FDA's benefit-risk assessment, particularly the understanding of the disease and its severity and the adequacy of existing treatment options. Therefore, FDA committed to hold at least 20 public meetings over the 5-year period, with each meeting focused on obtaining direct patient input in a specific disease area. This initiative, referred to as "patient-focused drug development," has since been described as potentially transformational in advancing the role of the patient in drug development and decisionmaking. Although initially committing to conduct 20 meetings, FDA is on track to conduct 24 meetings each in different disease areas. The goal of the meeting is to hear from patients and their caregivers about the impact of their disease on their lives, and for FDA to hear more about what treatment benefits would be most meaningful to patients, and what treatment burdens are most important to consider. Following each meeting FDA develops a *Voice of the Patient* report to capture what was heard in the meetings (and comments from patients received in the docket); these documents serve as a valuable reference for FDA reviewers in subsequent drug reviews and related decisionmaking.

Patient-focused drug development has provided key learnings for FDA that are being carried forward and integrated into our methods and approaches to development and decisionmaking. We recognize that patients with chronic serious disease are experts on what it is like to live with their condition, and we have learned that they want to be as active as possible in the work to develop and evaluate new treatments. In the past, patients' "chief complaints" were often not factored explicitly

into drug development plans (as endpoints and measures of drug benefit planned in trials), and this is an area of needed attention going forward. Although the PDUFA V patient-focused drug development initiative was intended as a pilot to elicit broader patient input, a key question for the agency was how to best build upon this pilot to advance the science and processes for effective incorporation of the patient’s voice in drug development and decisionmaking.

In preparing for PDUFA VI reauthorization discussions, FDA has worked to build on the successes and learnings of PDUFA V and pursue new areas of opportunity for innovation in the enhancement of regulatory decision tools and new potential sources of evidence to inform drug development and review.

PDUFA VI Reauthorization Process

Congress directed the Agency to reach out to all stakeholders to solicit thoughts and insights on PDUFA reauthorization and changes to PDUFA performance goals. FDA held an initial public meeting on July 15, 2015, which included presentations by FDA and representatives of different stakeholder groups, including patient advocates, consumer groups, regulated industry, health professionals, and academic researchers. A transcript and webcast recording are available on FDA’s website at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm>.

Based on comments to a public docket, and the Agency’s own internal analyses of program challenge areas, FDA developed a set of potential proposed enhancements for PDUFA VI and began negotiations with industry. Parallel discussions with public stakeholders were held monthly from September 2015—February 2016 to update participants on ongoing negotiations and solicit thoughts. Meeting minutes were posted on FDA’s website and are available at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm>.

A final public meeting was held on August 15, 2016, to discuss the PDUFA VI agreement and engage with interested parties on proposed recommendations. A summary of the agreement and a draft of the Commitment Letter were provided a month in advance of this discussion. Final PDUFA VI recommendations were transmitted to Congress in December 2016.

PDUFA VI Overview

Building on the success of previous agreements, PDUFA VI continues to support early and meaningful communication between FDA and drug sponsors to deliver safe and effective medications to Americans more quickly, and, expands on such communications by providing resources for the popular, highly successful, and resource-intensive Breakthrough Therapy program and streamlining review of products combining a drug or biologic with a device. It enhances drug development tools including biomarker qualification and provides resources to increase our understanding of how “real-world evidence” can be generated and used appropriately in regulatory decisionmaking. The agreement also enables us to leverage the use of real-world health data by enhancing the capabilities of FDA’s Sentinel System.

Many of these core provisions are explained in greater detail below.

Capturing the Patient Voice in Drug Development

Central to PDUFA VI, and its largest single investment component, are plans to elevate patient voices in developing new drugs to treat their diseases. The agreement shares the committee’s goals reflected in the 21st Century Cures Act (“Cures”)—and the highest priority of our stakeholders—to leverage essential patient input and insights to fight disease.

We are building on the success of PDUFA V which established the Patient-Focused Drug Development (PFDD) program to obtain valuable patient perspectives. Areas of focus were carefully chosen based on a public process soliciting patient and stakeholder input. Under PDUFA VI, we look forward to engaging in a transparent, multi-stakeholder approach that will lead to development of the methods and approaches to ensure patients not only become active participants but informants to industry drug development and agency review. The performance commitments and matching resources to sufficiently staff this critical new work are intended to bridge from patient-focused drug development meetings to fit-for-purpose tools to collect meaningful patient input, including capturing information on the natural progression of disease.

To help identify sound and rigorous methods to capture science-based, disease-specific patient input, FDA has committed to enhance its staff capacity, hold a series of four public workshops, and develop four key guidance documents on needed methods and approaches. The Agency will also publish on its website a repository of publicly available tools as a resource for stakeholders and ongoing efforts.

We are gratified by the enthusiastic response within the patient community to PFDD, and look forward to working with the broader community to advance the science of patient input—and deliver new and better treatment options.

Building a Solid Foundation for Breakthrough Therapies

The Breakthrough Therapy program, authorized by FDASIA, has become one of the most popular components of the human drug review program with requests and designations far exceeding expectations.

The increase in promising new drugs to treat serious and life-threatening diseases with unmet medical need is, of course, a very good thing for both patients and public health. But the growth of the BT program has strained limited available review staff resources. A hallmark of the BT program is intensive Agency interaction with sponsors during the development process on complex products with transformative potential. This “all hands on deck” approach provides a sponsor of a designated breakthrough product with guidance from the Agency on efficient drug development beginning as early as the Phase I period, an organizational commitment to involve senior managers, and eligibility for rolling review. Many of the BT designations granted so far have been for rare disease indications.

The PDUFA VI agreement provides dedicated funding to ensure the sustained success of the BT program. Additional resources will enable FDA to increase review staff and to supplement resources for clinical pharmacology, statistics, and product quality. This renewed commitment will enable the Agency to continue to work closely with sponsors to ensure expedited development and review of breakthrough therapies for serious or life-threatening diseases.

Advancing Biomarker Development

FDA and industry share the goals of Cures to accelerate development of reliable biomarkers to advance important new therapies. Biomarkers are currently used throughout the drug development process, including as surrogate endpoints to support earlier evidence for regulatory decisionmaking when evidence from a clinical endpoint could take much longer or require many more patients to be studied.

FDA commonly uses surrogate endpoints in accelerated approvals where confirmatory evidence is required to verify the expected clinical benefit after marketing begins. Surrogate endpoints have been the basis for 60 percent of rare-disease approvals. Once a surrogate endpoint is well-established to predict clinical benefit, surrogate endpoints can be used to support traditional approvals as well. For example, FDA regularly relies on a surrogate endpoint for approval of new therapies for diabetes (the HbA1C test, a measurement of hemoglobin with attached sugar in the blood that reflects the extent and persistence of elevated blood sugar) greatly expanding patient treatment options.

The PDUFA VI proposed enhancements include some of the same activities specified in Cures. PDUFA VI addressed the opportunity for application of biomarkers in two different areas, one involving proprietary use of a biomarker as a surrogate endpoint in a specific drug development program, and the other involving the more public process of biomarker qualification as a drug development tool.

FDA recognizes that early consultation can be important to an efficient development program when a sponsor intends to use a biomarker as a new surrogate endpoint that has never been used as the primary basis for product approval in the proposed context of use. The PDUFA VI commitments therefore provide for early consultation with the sponsor to enable the FDA review team to consult with senior management to evaluate the sponsor’s proposal before providing advice to the sponsor on a critical aspect of their development program. This will enable FDA to discuss the feasibility of the surrogate as a primary endpoint, any knowledge gaps, and how these gaps should be addressed before the surrogate endpoint could be used as the primary basis for approval.

PDUFA VI also provides enhancements for the more public drug development tool qualification pathway for biomarkers. The biomarker qualification program was established to support FDA’s work with external partners to develop biomarkers that aid in the drug development process. To facilitate the enhancement of the drug development tools qualification pathway for biomarkers in PDUFA VI, FDA proposes to convene a public meeting to discuss taxonomy and a framework with standards for biomarkers used in drug development, to develop guidance on biomarker taxonomy, contexts of uses, and general evidentiary standards for biomarker qualification, and to maintain a public website to communicate a list of biomarker qualification submissions in the qualification process.

Meaningful progress in developing additional biomarkers for public qualification requires collaboration among a wide range of stakeholders. FDA will continue to

work with the National Institutes of Health, the Biomarkers Consortium, the Critical Path Institute and others to advance biomarker development.

Streamlining Combination Product Review

More streamlined oversight of combination products is another FDA and industry priority reflected in PDUFA VI. Under the proposed enhancements FDA will pursue improvements in inter-center and intra-center combination product review coordination and transparency for PDUFA products that are combination products regulated by CDER and CBER (PDUFA combination products). FDA proposes to enhance staff capacity and capability across the relevant medical product centers and the Office of Combination Products to more efficiently, effectively, and consistently review combination products. FDA also proposes to streamline the process for combination product review and to improve the Agency's ability to track combination product review workload, including a third party assessment of current practices for combination drug product review.

Our goal, consistent with Cures, is to enhance the overall efficiency, consistency, and predictability of combination product review without imposing new administrative burdens.

Under PDUFA VI enhancements FDA will also establish new performance goals and submission procedures for the review of human factors protocols for PDUFA combination products. These goals will be to provide the sponsor with written comments on these protocols within 60 days of receipt. The goals to provide written comments within 60 days will begin at the 50 percent level in fiscal year 2019, and increase to 90 percent by fiscal year 2021.

Advancing the Use of Complex Innovative Trial Designs and Model Informed Drug Development

FDA routinely works closely with industry to facilitate innovative approaches to drug development that maintain our high standards for drug safety and efficacy. PDUFA VI promises to encourage future efforts by advancing Model-Informed Drug Development (MIDD) and the use of complex innovative and adaptive clinical trial designs.

The development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources can be used to inform regulatory decisionmaking, for example, in determining patient selection in clinical trials, individualized dosing for specific populations, or the need for post-marketing studies. To facilitate the development and application of these approaches during PDUFA VI, FDA proposes to convene a series of workshops to identify best practices for MIDD, to conduct a pilot program, to develop guidance on MIDD, and to update policies and procedures, as appropriate, to incorporate guidelines for the evaluation of MIDD approaches.

To facilitate the advancement and use of complex adaptive, Bayesian, and other novel clinical trial designs during PDUFA VI, FDA proposes to convene a public workshop on complex innovative trial designs, publish guidance on complex innovative trial designs, to conduct a pilot program, and to update policies and procedures as appropriate to incorporate guidelines on evaluating complex innovative trial designs.

Utilizing Real-World Observational Data

It has been said that medical care and biomedical research are in the midst of a data revolution, and networked systems, electronic health records, electronic insurance claims databases, social media, patient registries, and other new sources may comprise an immense new set of sources for data about health and healthcare. In addition, these "real-world" sources can provide data about patients in the setting of their environments—whether at home or at work—and in the social context of their lives. There is little doubt that the new sources of data now becoming increasingly available to researchers, clinicians, and patients hold enormous potential for improving the quality, safety, and efficiency of medical care. More work is needed to understand both the promise and pitfalls of far-reaching technological changes, including the multiple dimensions of quality and fitness for purpose for appropriate use of such data in regulatory decisionmaking.

FDA recognizes the potential value of utilizing "real-world" evidence in evaluating not only the safety of medications but also their effectiveness. To better understand how real-world evidence can be generated and used appropriately in product evaluation, FDA proposes to conduct one or more public workshops, as well as other appropriate activities (e.g., pilot studies or methodology development projects). Considering the available input, FDA will then publish draft guidance on how real-world evidence can contribute to the assessment of safety and effectiveness in regulatory submissions.

Under PDUFA VI, FDA also proposes to pursue a more well-established use of real-world evidence to support post market drug safety surveillance utilizing Sentinel. 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. FDA recently transitioned from the Mini-Sentinel pilot to the Sentinel System, but full utilization of the Sentinel System remains a work in progress. Continued development and integration of the Sentinel System is needed to realize the system's full value to the postmarketing safety review process.

To help realize the full value of the Sentinel System during PDUFA VI, FDA proposes to continue to expand the systems' data sources and core capabilities, to systematically integrate Sentinel into postmarketing review activities, to enhance communication practices with sponsors and the public regarding general methodologies for Sentinel queries, and to conduct an analysis of the impact of Sentinel expansion and integration for regulatory purposes.

Hiring and Retaining Highly Qualified Experts

To speed and improve development of safe and effective new therapies for patients requires that FDA hire and retain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews of human drug applications. In order to strengthen this core function during PDUFA VI, FDA proposes to commit to completing implementation of: a modernized position management system; corporate recruiting practices; augmenting capacity with contractor support; establishing a dedicated scientific recruiting function; setting metric goals for human drug review staff hiring; and conducting a comprehensive independent assessment of hiring and retention system performance. We want to thank you again for providing vital new hiring authority in Cures. Cures will greatly improve FDA's ability to hire and retain scientific experts in more complex and specialized areas and meet our growing responsibilities.

The hiring commitments proposed in PDUFA VI will complement Cures by supplementing the expertise and resources the Agency needs to perform its vital prescription drug mission.

Enhancing Management of User Fee Resources

FDA is committed to enhancing management of PDUFA resources and ensuring PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. In PDUFA VI, the Agency proposes to establish a resource capacity planning function to improve its ability to analyze current resource needs and project future resource needs, modernize its time reporting approach, conduct an evaluation of PDUFA program resource management, and publish a 5-year PDUFA financial plan with annual updates.

In addition, under PDUFA VI, FDA proposes to enhance the program fee structure and related mechanisms, to achieve increased predictability, stability, and efficiency. The current overall PDUFA fee structure and the fee setting process were established in 1992. Both FDA and industry recognize that updating some elements of the fee structure and the fee setting process will enhance administrative efficiency and the predictability and stability of fee amounts and revenues and improve FDA's ability to engage in long-term financial planning. FDA proposes to shift a greater proportion of the target revenue allocation to more predictable fee-paying types (20 percent to applications; 80 percent to Program fees), and make other modifications to improve efficiency and stability including discontinuation of the establishment and supplement fees, modifying the annual fee billing date to minimize the need for multiple billing cycles, and other technical changes.

We are incredibly proud of the progress FDA has made to speed medical products to patients through the PDUFA program, and look forward to working with Congress and industry to significantly further progress.

MDUFA

Enacted by Congress in 2002, MDUFA is a user fee program through which medical device companies pay fees to FDA when they submit a request for marketing authorization or register their establishments with FDA. The program includes commitments between the U.S.-medical device industry and FDA to improve the predictability, transparency, and consistency of regulatory processes, which are intended to reduce the time for FDA to make a decision about whether to authorize marketing of a device.

MDUFA has been reauthorized every 5 years since Congress created the program. As the program has evolved, FDA and industry have successfully negotiated agreements to improve patient access to medical devices and streamline regulatory processes.

During the 2012 MDUFA III testimony, many of you may recall that the program was in a much different place:²

- In fiscal year 2009, it took an average of 427 days to reach a decision on a pre-market approval application (PMA), the submission type required for the highest risk devices.
- In fiscal year 2010, it took an average of 150 days to reach a decision on a pre-market notification submission (also known as a 510(k)), the submission type required for low- to moderate-risk devices.

Thanks to the investment provided by industry, and direction provided by Congress, we have made substantial progress toward reducing decision times. As of 2015:

- It took an average of just 276 days to reach a decision on a PMA, a 35 percent decrease in 6 years; and
- It took an average of just 133 days to reach a decision on a 510(k), an 11 percent decrease in 5 years.

Further, we went beyond our MDUFA III commitments to reduce the median time to approve an Investigational Device Exemption (IDE) study to just 30 days in fiscal year 2015, down from 442 days in fiscal year 2011—a 93 percent decrease in 4 years. This improvement has allowed companies to begin their clinical trials earlier so they can begin collecting data to support a decision on their submission requesting marketing authorization. In addition, we reduced the average time to reach a decision on a *De Novo* classification request, the submission type typically used by novel low- or moderate-risk devices, to 259 days in fiscal year 2014, down from 770 days in fiscal year 2009—a 66 percent decrease in 5 years.

Changes we have made at CDRH to our culture, policies, and processes—in addition to user fee funding and changes to Federal law—have resulted in an improved medical device pipeline and innovative technologies being introduced in the United States earlier than in the past. For example, since 2009, the number of innovative devices we have approved has almost quadrupled. In 2016, we approved 91 innovative devices—the highest of any year since the user fee program began in 2003. In 2015, we approved the second highest number of innovative devices.

An example of an innovative technology that FDA approved first in the world is the “artificial pancreas,” something many members of this committee supported. Working interactively with the device manufacturer from the earliest stages of development to assist in making this technology available as quickly as possible, FDA approved the first device in the world that is intended to automatically monitor glucose levels around the clock and automatically provide appropriate insulin doses.

While we have made progress in many areas, we also recognize that more work remains and there are additional opportunities for improvements. We look forward to working with industry and Congress to ensure there are sufficient user fees resources as we strive to make these improvements. MDUFA IV agreement includes a new quality management program that will enhance consistency and predictability in pre-market review processes.

MDUFA IV agreement would also allow FDA to move forward in some critical and strategic areas such as strengthening our partnerships with patients.³ Strengthening patient input will allow us to promote more patient-centric clinical trials, advance benefit-risk assessments that are informed by patient perspectives, and foster earlier access to new devices.

Another critical area supported by the MDUFA IV agreement is the development of the National Evaluation System for health Technology, or NEST.⁴ The NEST is system-owned and -operated by multiple stakeholders that will use real-world data collected as part of routine clinical care. A robust NEST will enable manufacturers to harness real-world evidence that could enable them to drive down the time and cost of bringing a new device to market, expand the indications for already approved devices, and meet postmarket reporting requirements. The NEST will also enable faster identification of safety issues, reducing harm to patients and liability for companies.

The MDUFA IV agreement, which was supported by a broad array of stakeholders during the public review of the draft agreement, will expedite the availability of innovative new products, and its enhancements will continue to increase the efficiency

²See Appendix A: “U.S. Food and Drug Administration, Center for Devices and Radiological Health: Progress in Achieving Our Vision of Patients First.”

³See Appendix B: “Center for Devices and Radiological Health (CDRH): 2016–2017 Strategic Priorities—2016 Accomplishments.”

⁴See Appendix B: “Center for Devices and Radiological Health (CDRH): 2016–2017 Strategic Priorities—2016 Accomplishments.”

of FDA's programs. Improvements in total time to decision, transparency, consistency, and predictability will benefit industry, healthcare providers, and, most importantly, patients.

GDUFA

The remarkable success of the GDUFA program demonstrates how FDA, industry and other stakeholders can work together to achieve tremendous results. GDUFA has expanded access to affordable generic medicines. About 25 percent of all generic drugs that FDA has ever approved were approved in the past 4 years. At the same time, GDUFA helps assure the quality of generic drugs. Patient confidence that generic drugs will work the same as brand products, and can be freely substituted, is the foundation for trillions of dollars in savings that generics produce for the healthcare system.

Historically, the generic drug program has been a great success. The generic drug industry has grown from modest beginnings into a major force in healthcare. According to the QuintilesIMS Institute, generic drugs now account for 89 percent of prescriptions dispensed in the United States, and saved the U.S. healthcare system \$1.46 trillion from 2005 to 2015.

This success brought new challenges. Over the last several decades, the generic industry, the number of generic drug applications, and the number of foreign facilities making generic drugs grew substantially. As a result, FDA's generic drug program became increasingly under-resourced. Its staffing did not keep pace with the growth of the industry.

Solution: GDUFA. After much negotiation, FDA and the generic drug industry, in consultation with other stakeholders, developed a proposal for a generic drug user fee program and submitted it to Congress. Congress enacted it (GDUFA I) as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).

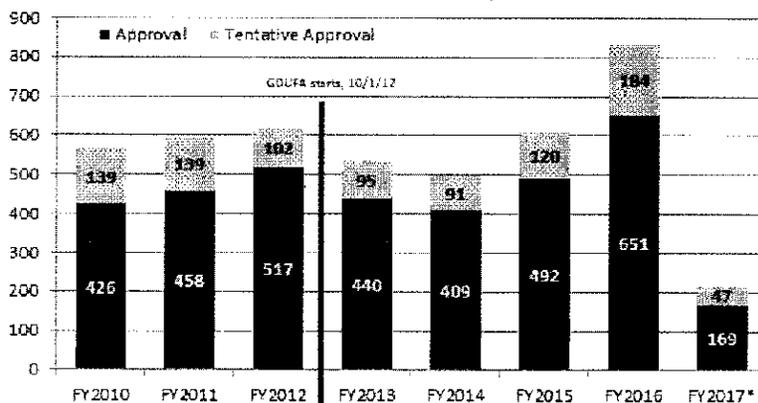
Under GDUFA I, industry agreed to pay approximately \$300 million in fees each year of the 5-year program. In exchange, FDA committed to performance goals, including a commitment to complete reviews in a predictable timeframe.

GDUFA Achievements

Met or Exceeded All Submission Review Goals to Date. FDA met or exceeded all GDUFA review goals to date, including goals for original Abbreviated New Drug Applications (ANDAs), ANDA amendments, Prior Approval Supplements (PAS), and controlled correspondence.

Record Increase in Approvals. In fiscal year 2016, FDA approved or tentatively approved 835 ANDAs. This was the most approvals ever in 1 year. Our previous high was 619.

Figure 8. FY2016 – A Record Year
Approvals and Tentative Approvals



*As of 3/1/17. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Expanded Consumer Access to Quality, Affordable Generic Medicines. As noted previously, approximately 25 percent of all currently approved generic drugs were approved over the past 4 years.

Prioritization and Approval of “First Generics.” FDA expedites the review of potential “first generic” ANDAs because they can open the market to generic competition for the first time. Most “first generic” ANDAs cannot lawfully be filed until a specific date, either 4 or 5 years after the innovator drug was approved. On this date, FDA often receives a bolus of ANDAs, from many different applicants. Beginning October 2014, in accordance with GDUFA I, these ANDAs received goal dates. We worked hard to review ANDAs for first generics even faster, expediting their review like an express line at the supermarket. For example, last year we had timely approvals of nine generic versions of Crestor, a cholesterol drug with approximately \$5 billion in annual sales. Significant first generic approvals for 2016, and the indications (abbreviated) for which these products were approved, are listed in the following text box.

| Significant First Generic Approvals for Calendar Year (CY) 2016 | |
|---|--|
| Brand (Generic Name) | Indication |
| Namenda (Memantine Hydrochloride) Extended Release | Alzheimer’s Disease |
| Nasonex (Mometasone Furoate) Nasal Spray | Allergies |
| Tamiflu (Osetamivir Phosphate) | Influenza A and B |
| Crestor (Rosuvastatin Calcium) | High cholesterol |
| Ammonul (Sodium Phenylacetate and Sodium Benzoate) | Acute hyperammonemia and associated encephalopathy <ul style="list-style-type: none"> • Approved for Orphan Indication • Acute hyperammonemia is life-threatening emergency that can rapidly result in brain damage or death |
| Benicar (Olmesartan Medoxomil) | High blood pressure |
| Seroquel XR (Quetiapine Fumarate) | Schizophrenia; Bipolar Disorder |
| Cellcept (Mycophenolate Mofetil Hydrochloride) Injectable | Prevent organ rejection for kidney, heart, or liver transplants |
| Emend (Fosaprepitant Dimeglumine) | Chemotherapy-associated nausea and vomiting |
| Sprycel (Dasatinib) | Cancer (Chronic Myeloid Leukemia) |
| Treanda (Bendamustine Hydrochloride) | Cancer (Chronic Lymphocytic Leukemia) |
| Sustiva (Efavirenz) | HIV-1 infection |
| Kaletra (Lopinavir and Ritonavir) | HIV-1 infection |
| Tikosyn (Dofetilide) | Atrial fibrillation/flutter |
| Banzel (Rufinamide) | Seizures |

Increase in First Cycle Approvals. Prior to GDUFA, ANDAs were approved in one review cycle less than 1 percent of the time. Now, approximately 9 percent of ANDAs are approved in the first review cycle.

Expanded Communications. To facilitate generic drug approval, in CY 2016 the Agency sent product developers approximately 1,800 communications and ANDA applicants approximately 6,600 communications. The Agency also issued 158 product-specific guidances, identifying methodologies for developing drugs and generating evidence needed to support generic approval. These guidances help companies de-

velop ANDAs that will meet FDA's regulatory expectations. Over 1,500 product-specific guidances are currently available as resources for prospective applicants.

Risk-Based Inspection Parity. Before 2012, the law required us to inspect domestic facilities at a 2-year interval, but was silent on frequency for foreign facilities, regardless of their relative risk. Since 2012, FDASIA directed us to target inspections globally on the basis of risk. Many ANDAs rely on third-party facilities to manufacture active pharmaceutical ingredients or perform other roles in product development, and many of these facilities are located outside of the United States. Thanks to GDUFA, we have achieved the goal of risk-based inspection parity for foreign and domestic facilities.

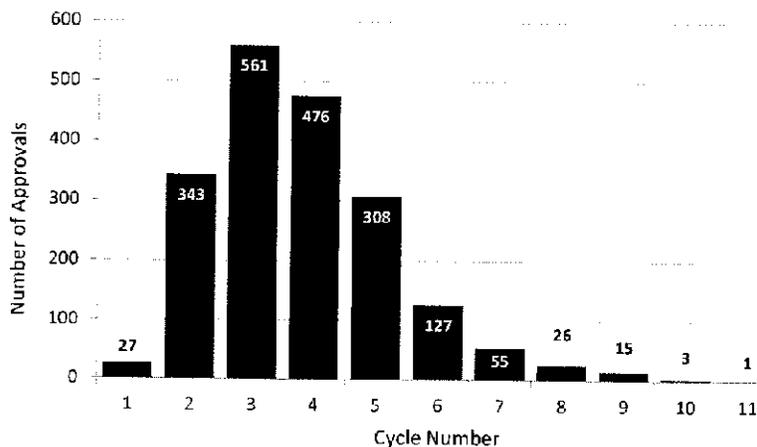
How did FDA achieve these results?

Deep, foundational restructuring. We achieved these results by building a modern generic drug program to comply with our commitments in GDUFA I. This involved major reorganizations. We reorganized the Office of Generic Drugs and elevated it to "Super-Office" status, on par with the Office of New Drugs. We established a new Office of Pharmaceutical Quality to integrate the quality components of ANDA review. FDA's Office of Regulatory Affairs also made significant inspection program enhancements. In addition, we re-engineered our business processes, developed an integrated informatics platform to support the review process, and hired and trained over 1,000 new employees.

Current Challenges

We do have some ongoing challenges. The first challenge relates to submission completeness. Historically, it has taken on average about four review cycles to approve an ANDA as a result of deficiencies by generic drug sponsors in submitting complete applications.

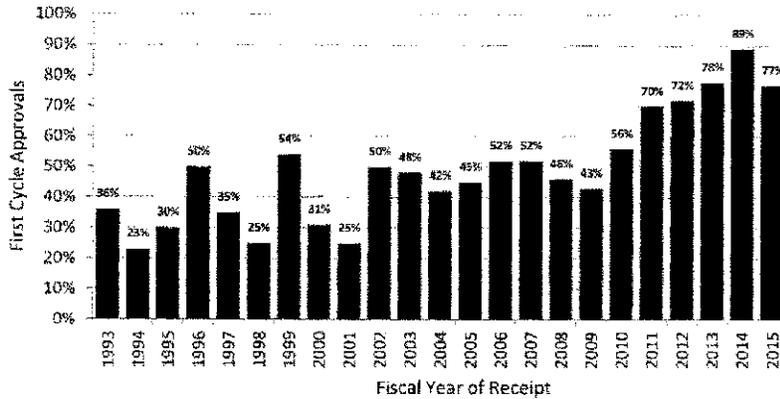
**Figure 9. Review Cycles for ANDAs
2009 through July 2014**



This has resulted in the submission of numerous amendments to applications by the companies to correct deficiencies in the original ANDAs, and comprises a huge amount of re-work for FDA and industry alike. Currently, about 1,800 applications are back with industry awaiting resubmission to correct deficiencies in the original application. More work by both FDA and industry will be necessary to have the filings be "right the first time."

Improvement may take some time. In the first few years of the Prescription Drug User Fee Act (PDUFA) program, the first cycle approval rate for new drugs was as low as 23 percent. Now it is about 80 percent on average. Achieving this was the result of many years of cooperative work by the Agency and industry in establishing standards and meeting these expectations.

**Figure 10. First Cycle Approval Rate Under PDUFA
CDER NME NDAs/BLAs†
First Action Approval Rate**



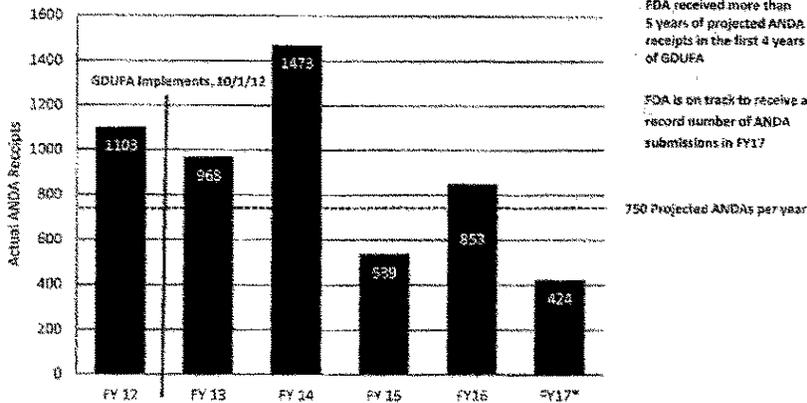
Data as of 12/9/2016

† Multiple applications pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

‡ Original BLAs that do not contain a new active ingredient are excluded. Percentages exclude pending applications from the denominator.

The second challenge relates to the volume of applications. We received many more applications than expected. As the GDUFA I Commitment Letter stated, GDUFA I review goals and planning were based on the assumption that FDA would receive approximately 750 ANDAs per year. We budgeted and planned with this projection in mind. However, in fiscal years 2012, 2013 and 2014, we received over 1,000 ANDAs—nearly 1,000—and nearly 1,500 applications, respectively. As discussed below, GDUFA II would have a program size commensurate with the Agency's overall ANDA workload.

Figure 11. Projected vs Actual ANDA Receipts



FDA received more than 5 years of projected ANDA receipts in the first 4 years of GDUFA

FDA is on track to receive a record number of ANDA submissions in FY17

* As of 12/31/16. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Third, several factors can delay timely consumer access to less expensive generic medicines. These factors include:

- inappropriate use of statutory requirements regarding single-shared system Risk Evaluation and Mitigation Strategies (REMS) to delay generics entry to the market;
- delaying or denying generic companies' access to reference-listed drug products, thereby preventing the companies from conducting studies required for approval; and
- misuse of FDA's citizen petition process as a means to block generic approvals.

Reauthorization

Faster review of priority ANDAs. GDUFA II would establish faster review of priority submissions. Priority review would be available for submissions that FDA considers to be public health priorities pursuant to CDER's Manual of Policies and Procedures (MAPP) 5240.3 Rev. 2, *Prioritization of the Review of Original ANDAs, Amendments and Supplements*, as revised (the CDER Prioritization MAPP). In the final year of GDUFA I, all ANDAs receive a review goal of 10 months. In GDUFA II, standard ANDAs would continue to be reviewed within 10 months of submission, but priority ANDAs would be reviewed within 8 months of submission. To help ensure the more aggressive 8-month timeline can be met, for each priority review, the applicant would have to submit a pre-submission facility correspondence (PFC) listing all of the facilities that will require FDA inspection at least 2 months prior to the date of ANDA submission.

FDA and the generic drug industry agreed to an 8-month priority review goal for two main reasons. First, it is the shortest time feasible given the global nature of generic drug manufacturing. In most cases, before the ANDA can be approved, FDA needs to inspect one or more manufacturing facilities to confirm that the drug will meet quality standards. Many ANDA applicants rely on multiple overseas manufacturing facilities, and conducting inspections of facilities in foreign countries requires additional time for FDA inspectors to obtain State Department approval and country-specific visas, and to meet other travel-related requirements. By providing FDA with information about the manufacturing facilities in advance of the ANDA submission, the PFC would give the Agency critical lead time to determine whether facility inspections will be needed, and when they are, to initiate travel planning.

Second, 8 months is enough time for FDA to communicate—and applicants to correct—application deficiencies, so a priority ANDA can be approved in the current review cycle, not a later review cycle. A goal date set at fewer than 8 months would wind down work just when it is gaining momentum. Applicants would not have time to make corrections and thus get their ANDAs approved. To resolve outstanding issues, an additional cycle of review would be necessary. Approval would be delayed for at least 6 to 10 more months, depending on how quickly the applicant could develop an amendment and the GDUFA II review goal for the specific type of amendment submitted.

Pre-ANDA Program Enhancements. To reduce the number of cycles to approval, particularly for complex products, GDUFA II would establish a pre-ANDA program. It would clarify regulatory expectations for prospective applicants early in product development and help applicants develop more complete submissions, thus promoting a more efficient and effective review process.

The GDUFA II pre-ANDA program would establish three types of meetings for complex products. In a product development meeting, FDA would provide targeted advice concerning an ongoing ANDA development program. Pre-submission meetings would give applicants an opportunity to discuss and explain the content and format of an ANDA before it is submitted. Mid-review-cycle meetings would occur post-submission, after the last key review discipline has communicated deficiencies, and would enable applicants to discuss current concerns and next steps. FDA intends to issue a guidance concerning the pre-ANDA program, setting forth meeting policies and procedures. In addition, the Agency intends to establish metric goals for product development and pre-submission meetings.

For products that are not complex, GDUFA II would direct the Agency to establish metric goals for FDA to issue product-specific guidance. Product-specific guidance identifies the methodology for developing generic drugs and generating evidence needed to support generic approval. They help companies develop ANDAs that will meet FDA's regulatory expectations. In addition, the pre-ANDA program would enhance controlled correspondence, regulatory science, the Inactive Ingredient Data base, and Safety Determination Letters.

ANDA Review Program Enhancements. GDUFA II would further refine and modernize the ANDA review process from start to finish.

The GDUFA II ANDA review program would start with submission of an ANDA. When an ANDA is submitted, FDA first determines whether an ANDA is sufficiently complete to permit a substantive review. If it is sufficiently complete, then

FDA “receives” it within the meaning of the statute. FDA would aspire to make these receipt determinations within consistent deadlines. The Agency also would increase receipt-related communications in an attempt to fix applications and resolve certain receipt disputes within consistent timelines.

When the ANDA has been received and is under review, pursuant to GDUFA II, FDA would communicate review deficiencies beginning at about the mid-point of the review. Then, communications would continue on a rolling basis. In GDUFA I, many deficiencies were communicated at the very end of the review, in the form of a Complete Response Letter, too late for the applicant to fix them. This produced additional cycles of review, and delayed approval. By contrast, GDUFA II would use “real time” communications to give applicants more opportunities to correct deficiencies in the current review cycle.

To support product launches and business planning that can improve access to generics, Regulatory Project Managers (RPMs) would provide review status updates and certain other types of notifications. The Agency would also establish new technical procedures to facilitate approval of tentatively approved ANDAs on the earliest lawful approval date.

When deficiencies in an ANDA prevent FDA from approving it, FDA issues a Complete Response Letter (CRL) itemizing deficiencies that must be corrected for the ANDA to be approved. GDUFA II would establish post-CRL teleconferences to allow applicants to seek clarification concerning deficiencies identified in CRLs. This would help applicants meet FDA’s expectations when an ANDA is re-submitted for additional review. There would be metric goals for such teleconferences, and for formal dispute resolutions.

Finally, in GDUFA I, different cohorts and tiers of submissions received very different goals. The scheme was challenging for FDA to operationalize and administer. In addition, there was a significant gap between the negotiated commitments and stakeholder expectations. We appreciate that this has been an understandable area of concern for all of us. In GDUFA II, all ANDAs and ANDA amendments would fall within a single, consolidated review goals scheme. This would simplify and streamline GDUFA operations, and better align commitments with expectations.

Drug Master File (DMF) Review Program Enhancements. DMFs are submissions that provide FDA with confidential information about facilities, processes, or articles used to manufacture, process, package, or store drugs. They support approval of ANDAs and are often submitted by API manufacturers that sell to ANDA sponsors. The commitment letter that accompanies GDUFA II contains five significant DMF review program enhancements.

Facility Assessment Enhancements. As previously mentioned, FDASIA eliminated longstanding minimum inspection frequency requirements and, instead, directed FDA to inspect drug facilities globally on the basis of risk. The transition to this new paradigm has been commercially disruptive for industry, which over time had developed expectations and business processes based on the old model. To mitigate export-related challenges identified by U.S.-based active pharmaceutical ingredient (API) manufacturers, GDUFA II would require FDA to issue guidance and conduct outreach to foreign regulators on the risk-based selection model and take steps to support exports. To mitigate ANDA sponsor concerns, FDA would enhance the speed and transparency of communications concerning facility assessment, and generally update and seek feedback from industry. In addition, to enhance transparency concerning GDUFA facilities and sites, FDA would update its existing, publicly available facility compliance status database.

Accountability and Reporting Enhancements. In GDUFA II, enhanced infrastructure and analytics would increase transparency and accountability and strengthen program management and resource use. FDA would develop internal capacity to enable improved productivity and performance through regular assessment of progress toward GDUFA II goals and transparent, efficient administration, allocation and reporting of user fee resources. In addition, an independent third party would evaluate the program.

FDA would expand GDUFA program reporting on a monthly, quarterly and annual basis. Robust performance reporting would enable Congress, industry and other stakeholders to gauge the generic drug program’s performance.

Program Size Commensurate with Overall ANDA Workload. ANDAs are the primary workload driver of the generic drug program. In GDUFA I, the number of submissions received substantially exceeded projections. In order to maintain productivity and implement proposed GDUFA II improvements, FDA and the generic drug industry agreed that user fees should total \$493.6 million annually, adjusted for inflation.

Modification of User Fee Structure. For program stability, user fee collections must be predictable. Application volume can fluctuate from year to year, but there

is a relatively stable universe of generic drug facilities and ANDA sponsors. To maintain a predictable fee base and better align responsibility with program costs and fee-paying ability, FDA and industry propose to shift the burden more toward annual program fees. Firms that sponsor one or more approved ANDAs would pay an annual fee. In addition, Finished Dosage Form (FDF) and API facilities would continue to pay annual fees as they did in GDUFA I.

In GDUFA I, ANDA sponsors making changes to an already approved ANDA through a Prior Approval Supplement (PAS) were required to pay a PAS application fee. The volume of PASs is unpredictable. Collecting the fees was resource intensive. The new ANDA program fee is meant to be an investment in the program, and includes the cost of reviewing PAS submissions. For these reasons, FDA and industry propose to eliminate the PAS fee.

Small Business Considerations. GDUFA II takes small business considerations into account. First, no facility or ANDA sponsor would be charged an annual fee until an ANDA in which it is listed is approved. This eliminates a situation that occurred in GDUFA I, where a company could be charged an annual fee, sometimes for several years in a row, even though no ANDA linked to the facility had been approved yet. Second, the annual program fee would have three tiers—small, medium and large—based on the number of approved ANDAs owned by the firm and its affiliates. Third, Contract Manufacturing Organizations (CMOs are hired by ANDA sponsors to manufacture their generic drugs) would pay one-third the annual facility fee paid by ANDA holders.

In summary, FDA and the regulated industry, in consultation with other stakeholders, spent nearly a year developing the proposed GDUFA II agreement. It contains numerous, major reforms to address the main challenge facing the generic drug review program—namely, multiple review cycles. It is very inefficient for FDA and applicants alike to cycle through an ANDA over and over again. GDUFA II's pre-ANDA program, ANDA review program enhancements, and priority review program will increase the odds of first cycle approval, reduce the number of cycles to approval, and expand consumer access to quality, less expensive generic medicines. While we have made significant progress in our generic drug review, GDUFA II will support the agency in improving consumers' timely access to generic medicines.

BSUFA

FDA is supportive of and fully engaged with the development and approval of biosimilar and interchangeable products. Many of our most important drugs are biological products. Biological products are used to treat patients who have serious and life-threatening medical conditions including rheumatoid arthritis, diabetes, and cancer. It is important for the public health of the U.S. population to have access to safe, effective, and affordable biological products. Biosimilars can provide more treatment options for patients, and possibly lower treatment costs, enabling greater access for more patients.

To earn and sustain both physicians' and patients' confidence in biosimilar and interchangeable products, FDA is applying a scientifically rigorous review process and approval standard. Healthcare providers and patients have consistently emphasized that FDA's approval of biosimilars should provide assurance that biosimilars will have the same clinical performance as the originator, or reference product. FDA is committed to providing this assurance, and recognizes its importance to the uptake and acceptance of these products, and the future success of the biosimilars program.

Biologics Price Competition and Innovation Act (BPCI Act) and Biosimilar User Fee Act (BsUFA): Important Additions to FDA Statutory Authority

BPCI Act. The Biologics Price Competition and Innovation (BPCI) Act established a new abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. With this abbreviated approval pathway, an applicant can get a biosimilar approved by demonstrating, among other things, that it is highly similar to a reference biological product already licensed by FDA. Biological products are made from living organisms and usually consist of large, complex molecules that cannot be easily copied, in contrast to "small molecule" drugs that generally are produced through chemical processes and can be replicated as "generic" drugs. Unlike generic drugs, biosimilars must be highly similar to, not the same as, the reference product to which they are compared. While biosimilars may have certain allowable differences from the reference product, the applicant must demonstrate that there are no clinically meaningful differences between the biosimilar and its reference product in terms of safety, purity and potency.

The abbreviated approval pathway permits a biosimilar application to rely, in part, on FDA's previous determination that the reference product is safe and effective, saving the applicant time and resources and thereby encouraging price competition and lowering healthcare costs. The ongoing and future impact of this relatively new law is significant. FDA's biosimilars program has sparked the development of a new segment of the biotechnology industry in the United States. The growth of this new market segment should expand opportunities for technical innovation, job growth, and patient access to treatment.

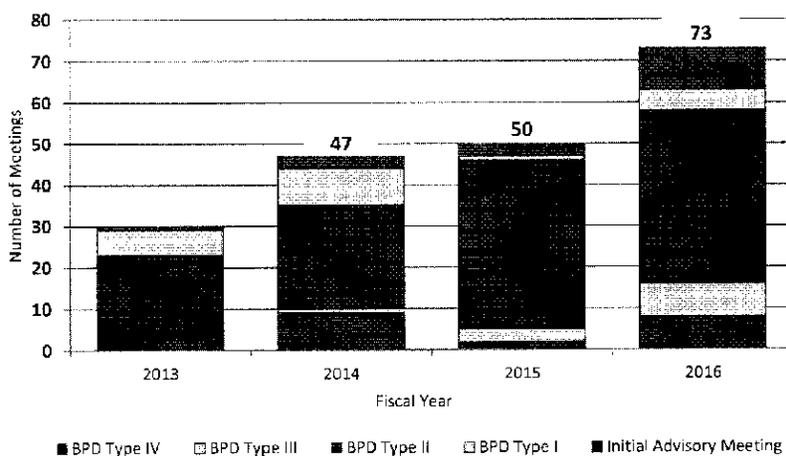
BsUFA I. The Biosimilar User Fee Act (BsUFA) was enacted as part of the FDA Safety and Innovation Act (FDASIA) (Public Law No. 112-144, enacted on July 9, 2012). The first Biosimilar User Fee Agreement (BsUFA I) between the Agency and industry allowed FDA to begin development of the infrastructure needed to support this new program and devote additional resources to support the abbreviated development process leading to the approval of safe and effective biosimilar products for patients.

One of the first steps in the development and review process for a biosimilar is for an applicant to join FDA's Biosimilar Product Development (BPD) Program. The BPD Program was created as a part of BsUFA I to provide a mechanism and structure for applicants to engage with FDA during the development of a biosimilar. As of February 2017, 64 programs were enrolled in the BPD Program and CDER has received meeting requests to discuss the development of biosimilars for 23 different reference products.

In engaging with sponsors regarding biosimilar development, CDER holds development-phase meetings and provides written advice for ongoing development programs. These meetings include a Biosimilar Initial Advisory meeting where there is an initial discussion on whether licensure would be feasible for a particular product; and BPD meeting Types 1-4 where applicants can receive advice at different stages of product development. The meeting that is in highest demand and often requires significant review effort on behalf of FDA is the BPD Type 2 meeting where FDA conducts a substantive review of summary data and an applicant receives advice on specific issues. For additional details on the BsUFA BPD meeting types, please see Appendix C.

As shown in Figure 12, the total number of meetings scheduled has increased each year since the beginning of BsUFA I. Additionally, in order to provide ongoing support for BPD programs, FDA has provided written advice to sponsors in instances where meeting requests were denied or canceled due to incomplete or premature requests.

Figure 12. Number of BsUFA Program Meetings Scheduled
FY 2013 - FY 2016



The BPD meetings have provided valuable advice to biosimilar sponsors in the development of their products and associated biosimilar marketing applications. Since

program inception and as of February 2017, nine companies have publicly announced submission of 13 applications for proposed biosimilar products to FDA.

FDA approved the first biosimilar in the United States, Zarxio (filgrastim-sndz), a biosimilar to Neupogen, on March 6, 2015. In 2016, FDA approved three additional biosimilars: Inflectra (infliximab-dyyb), a biosimilar to Remicade; Erelzi (etanercept-szss), a biosimilar to Enbrel; and Amjevita (adalimumab-atto), a biosimilar to Humira.

Challenges

While we have made significant progress in creating and implementing this fairly new program, there is more work to do and, as with any new initiative, there are challenges that we need to address. These challenges in BSUFA I provide context for the discussions we had with industry during the BSUFA II negotiations. The ability to hire the right staff is critical to ensure the timely review of new biosimilars. While it's true that FDA has been somewhat limited in its capacity to recruit and retain the critical scientific, technical, and professional talent needed to address the complex and often novel scientific and legal issues involved in biosimilar review, we are committed to making meaningful and measurable progress.

The lack of additional staffing to handle the increased workload for biosimilar review also has impacted review performance. For example, in fiscal year 2015, FDA was able to schedule only 50 percent of Initial Advisory meetings within the 90-day meeting goal, only 67 percent of Type 1 meetings within the 30-day meeting goal, only 49 percent of Type 2 meetings within the 75-day meeting goal, and zero Type 4 meetings within the 60-day meeting goal. FDA's performance during fiscal year 2016 was an improvement from fiscal year 2015; however, FDA still faced challenges and was unable to meet some of the applicable performance goals. Despite the BsUFA I performance challenges, industry indicated that in BsUFA II, they would like to see more meetings and faster turnaround of Agency advice.

BsUFA II

FDASIA directed FDA to develop recommendations for BsUFA II for fiscal years 2018 through 2022. To develop these recommendations, FDA consulted with industry and public stakeholders, including scientific and academic experts, health care professionals, and patient and consumer advocates, as directed by Congress. In addition to meetings with industry organizations, FDA held two public meetings on December 18, 2015, and October 20, 2016, to obtain input from public stakeholders.

As discussed below, BsUFA II incorporates lessons learned from implementation of BsUFA I and provides a roadmap to successfully overcome some of the unexpected challenges encountered with BsUFA I.

Proposed Fees. At the time BsUFA I was authorized, the size and costs of the program were uncertain. As such, it was agreed that user fees for BsUFA I should be based off the fees established under the PDUFA program. As part of the recommendations for BsUFA II, FDA and industry agreed to establish an independent fee structure based on BsUFA program costs to generate a total of \$45 million in revenue for fiscal year 2018. FDA and industry representatives also propose that FDA can adjust this amount to reflect updated workload and cost estimates for fiscal year 2018 when FDA publishes the Federal Register (FR) notice establishing fee revenue and fees for fiscal year 2018. The adjustment cannot increase the target revenue more than \$9 million, and FDA must describe the methodology used to calculate the adjustment in the FR.

FDA's recommendations for the BsUFA II user fee structure include additional changes to enhance the predictability of BsUFA funding levels and sponsor invoices, minimize inefficiency by simplifying the administration of the program, and improve FDA's ability to manage program resources and engage in effective long-term planning. These changes include the removal of the supplement fee and establishment fee, while retaining the initial, annual, and reactivation biosimilar biological product development (BPD) fees. Under the recommendations, the product fee is renamed the BsUFA Program fee and includes a new provision that sponsors shall not be assessed more than five BsUFA Program fees for a fiscal year per application. These changes are consistent with changes proposed for the fee structure under PDUFA VI.

Under BsUFA II, FDA also would establish a capacity planning adjustment as well as an operating reserve adjustment. The capacity planning adjustment, once operational (expected in fiscal year 2021), would establish a mechanism to adjust the annual fee revenue target based on analytically demonstrated sustained changes in BsUFA workload. The operating reserve adjustment would provide the ability to further adjust up or down the annual fee revenue to ensure the program is adequately resourced to sustain operations, while also preventing the accrual of unrec-

essarily large carryover balances. Under BsUFA II, the \$20 million (adjusted for inflation) spending trigger would be considered to be met in any fiscal year if the costs funded by budget authority are not more than 15 percent below the inflation adjusted amount for that year. This flexibility, similar to the spending trigger provisions in PDUFA and GDUFA, will enhance FDA's level of certainty that it can allocate and spend the required amount of non-user fee funds for a given fiscal year and thereby spend user fee funds in that fiscal year.

Proposed Performance Goals. The BsUFA II commitment letter establishes an application review model similar to "the Program" established under PDUFA V for new molecular entity new drug applications and original biological licensing applications. This new model is intended to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval. The parameters of the Program will include the following: (1) pre-submission meeting, (2) original application submission, (3) Day 74 Letter, (4) review performance goals (10-month user fee clock starts at 60-day filing date), (5) mid-cycle communication, (6) late-cycle and advisory committee meetings, (7) inspections, and (8) assessment of the Program.

The additional 2-month review clock time (10 month plus 60 days, noted above) is intended to provide FDA more time to complete additional late cycle activities added as part of the new review model (e.g., late-cycle meeting) and address other late cycle review work, such as application deficiencies, Advisory Committee advice, and inspection issues to improve the efficiency of the first review cycle.

Under the BsUFA II commitment letter, Biosimilar Initial Advisory meetings will occur within 75 calendar days, instead of 90 days agreed to in BsUFA I, from receipt of the meeting request and meeting package. This type of meeting will be limited to a general discussion on whether a proposed product could be developed as a biosimilar and to provide high-level overarching advice on the expected content of the development program. To provide necessary time for FDA discussions and to develop comprehensive responses, BPD Type 2 Meetings will occur within 90 calendar days, instead of 75 days as in BsUFA I, from receipt of the meeting request and meeting package. There will be phased-in performance goals for meeting these deadlines of 80 percent in fiscal years 2018 and 2019 and 90 percent in fiscal years 2020 through 2022. In addition, the Agency will send preliminary responses to the sponsor's questions contained in the background package no later than 5 calendar days before the face-to-face, video conference or teleconference meeting date for BPD Type 2 and Type 3 meetings.

Proposed Guidance Development. While the BPCI Act states that there is no requirement for FDA to issue guidance before reviewing or taking an action on a biosimilar application, industry has indicated to FDA that guidances are an important product development tool. As part of its work to implement the BPCI Act, FDA has finalized six guidances and issued four draft guidances. The six guidances that are final are:

1. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (finalized on April 28, 2015).
2. *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* (finalized on April 28, 2015).
3. *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (finalized on April 28, 2015).
4. *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* (finalized on November 17, 2015).
5. *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (finalized on December 28, 2016).
6. *Nonproprietary Naming of Biological Products* (finalized on January 12, 2017).

Under the BsUFA II commitment letter, FDA has committed to publishing a revised draft guidance on *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* no later than September 30, 2018, and updating the draft guidance on *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* by December 31, 2018.

Additionally, under the BsUFA II commitment letter FDA has committed to publishing draft or final guidance describing the following:

- *Considerations in Demonstrating Interchangeability with a Reference Product* (draft on or before December 31, 2017, and revised or final guidance 24 months after close of the public comment period)
- *Statistical Approaches to Evaluate Analytical Similarity* (draft on or before December 31, 2017, and revised or final guidance 18 months after close of the public comment period)

- *Processes and Further Considerations Related to Post-Approval Manufacturing Changes for Biosimilar Biological Products* (draft on or before March 31, 2019, and revised or final guidance 18 months after the close of the public comment period)
- *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (draft guidance published in May 2014, revised or final guidance will be published on or before May 31, 2019)
- *Nonproprietary Naming of Biological Products* (draft guidance published in August 2015, revised or final guidance will be published on or before May 31, 2019)
- *Labeling for Biosimilar Biological Products* (draft guidance published March 2016, and revised or final guidance on or before May 31, 2019).

FDA has already published or finalized three of these guidances ahead of schedule: the draft *Considerations in Demonstrating Interchangeability with a Reference Product* and final guidance on *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product and Nonproprietary Naming of Biological Products*.

As with all review programs within FDA, the ability to hire and retain qualified staff is critical to ensure the availability of new safe and effective drugs and biologics. Congress included much-needed new hiring authorities in the recently enacted Cures bill. FDA looks forward to applying these new authorities to further improve our biosimilars program. Several FDA goals in the BsUFA II commitment letter support this process: FDA will strengthen staff capacity; modernize the hiring system and infrastructure; augment human resources capacity through the use of dedicated expert contractors; establish a dedicated function for the recruitment and retention of scientific staffing; set clear goals for hiring; and conduct a comprehensive and continuous assessment of hiring and retention practices. These enhancements will allow us to meet our performance goals which in turn will help us save the applicant time and resources and ultimately encourage price competition.

The Path Forward

BsUFA I provided critically needed funding for FDA to implement the beginning of a successful biosimilars program. We look forward to working with Congress and industry as we continue to strengthen this program and make improvements where needed. This relatively new pathway for biosimilar and interchangeable products has the potential to offer a significant contribution to the public health of many Americans by increasing access to more affordable biologics. At FDA, we are working hard to ensure this positive impact can be realized. We are optimistic and energized about the future of biosimilars.

Human drug user fees have revolutionized the drug review process in the United States since they were adopted 20 years ago for prescription drug products, allowing FDA to speed the application review process without compromising the Agency's high standards. User fees offer a strong example of what can be achieved when FDA, industry and other stakeholders work together on the same goal. User fees provide a critical way to ensure that FDA has the resources needed to conduct reviews in a timely fashion.

CONCLUSION

The FDA user fee agreements have revolutionized the drug and device review process in the United States since they were adopted, allowing FDA to speed the application review process without compromising the Agency's high standards. User fees offer a strong example of what can be achieved when FDA, industry, and other stakeholders work together toward the same goal. User fees provide a critical way to ensure that FDA has the resources needed to conduct reviews in a timely fashion. While we have made demonstrable progress in partnering to bring medical products to market in as timely a manner as possible, we know that more work remains to be done to further enhance and optimize our processes. The reauthorization of PDUFA, MDUFA, GDUFA, and BsUFA will allow FDA to build upon the demonstrated success of these programs, and in so doing, further benefit patients and affirm our Nation's standing as a global leader in biomedical innovation.

Appendix A

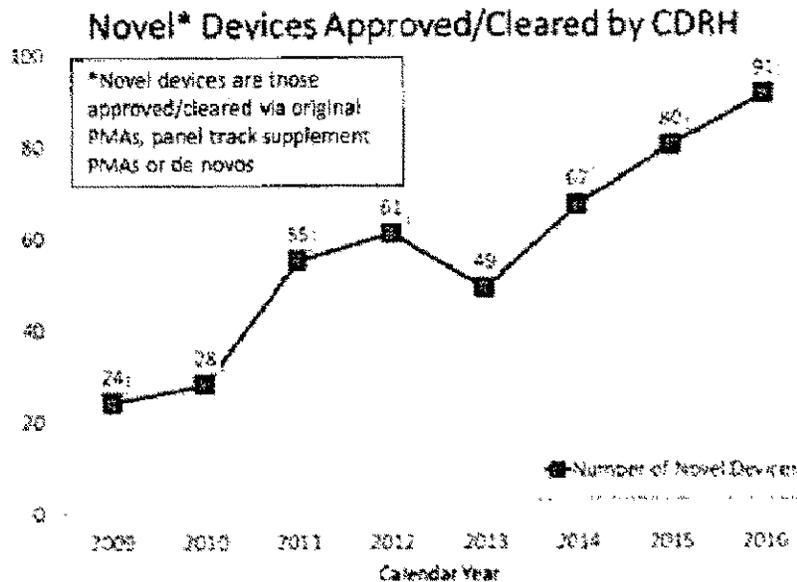
U.S. FOOD AND DRUG ADMINISTRATION CENTER FOR DEVICES AND RADIOLOGICAL HEALTH: PROGRESS IN ACHIEVING OUR VISION OF PATIENTS FIRST

In the early part of this decade, industry argued that FDA regulation hindered innovation and contributed to the growing number of device companies seeking marketing authorization for their devices abroad before introducing them in the United States, and the increasing gap between when a device is approved in another coun-

try and when it is approved in the United States. This reality, its adverse impact on patients, plus CDRH's own awareness of our declining performance over almost a decade, led CDRH to implement new programmatic changes. These changes, along with increased user fee funding and changes in Federal law have helped us strengthen our performance and better address the rapidly evolving field of medical device innovation. To guide us in our mission to improve the health and quality of life of patients, in 2012 we adopted a *new vision*⁵ to reflect this change in mindset, that: **Patients in the United States have access to high-quality, safe and effective medical devices of public health importance first in the world.**

DOING BUSINESS BETTER

Since late 2009, CDRH has continuously improved the way we do business through a series of culture, policy and process changes. This can be seen through our commitment to providing excellent customer service, new patient-centered paradigms, and our strong performance across a range of objective measures, including the time it takes to review several types of medical device submissions. These improvements are reflected by the **nearly four-fold increase in the annual number of novel medical device approvals.**



Fast Facts: CDRH oversees approximately **175,000 medical devices** on the U.S. market, more than **18,000 medical device manufacturers**, and more than **25,000 medical device facilities worldwide**. Each year we receive some 22,000 pre-market submissions (includes supplements and amendments) and more than **1.4 million reports on medical device adverse events and malfunctions**.

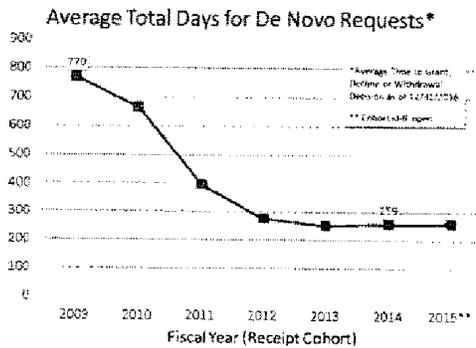
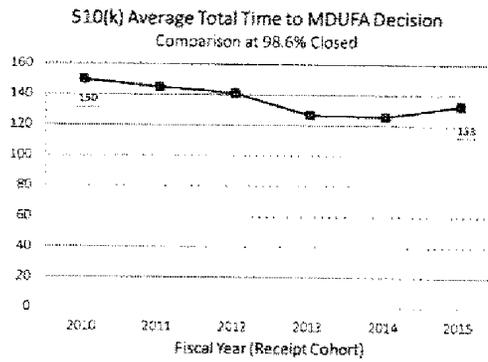
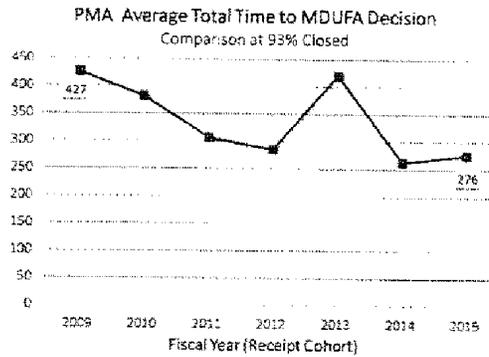
Time. Time, with its cost implications, plays a critical role in an innovator's decision as to whether and when to bring a new technology to the United States. What good is a new technology if patients do not have timely access to it? How helpful is a new technology that doesn't benefit patients or poses unacceptable risks? By reducing the time of every regulatory stage of the total product life cycle, including the review of medical device submissions, while still assuring robust but appropriate (least burdensome) evidence generation and high-quality decisionmaking, we help patients get access to safe and effective medical technologies and foster innovation. After steadily worsening performance from 2002 to 2010 on a variety of measures, including pre-market review times, CDRH has reduced the decision time on all key pre-market submission types.

⁵ CDRH Mission, Vision and Shared Values.

PMA. While pre-market approval applications (PMAs) only account for approximately 1 percent of all pre-market medical device submissions, they represent medical devices with the highest risk to patients (Class III devices) and, therefore, require more data and a more rigorous review by CDRH. In 2009, it took an average of 427 total days to reach a decision on a PMA. **By 2015, we had reduced the total decision time by 35 percent.**

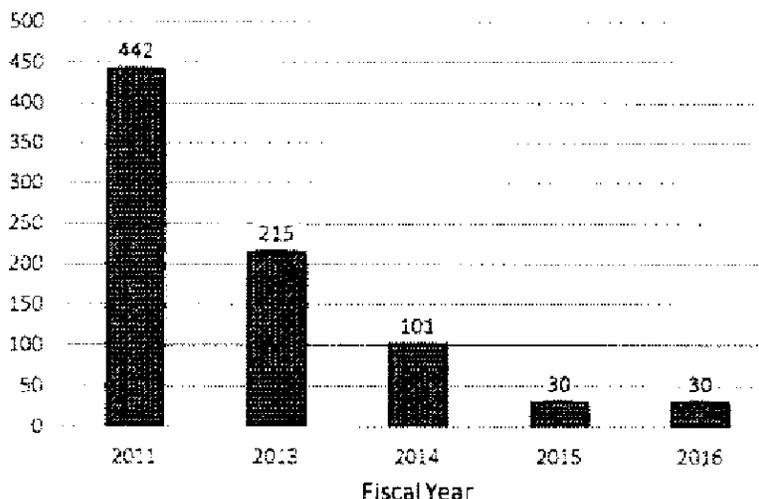
510(k). Named after its section number in Federal law, this category represents the bulk of pre-market submissions for medical devices. Manufacturers submit 510(k)'s to CDRH for devices with low to moderate risk to patients (Class II), and our review standard is based on substantial equivalence (whether a device is at least as safe and effective as a device already on the market). In 2010, it took an average of 150 total days to reach a decision on a 510(k). **By 2015, we had reduced the total decision time by 11 percent.**

De Novo. *De novo* classification is a pathway that enables manufacturers of certain low- to moderate-risk novel devices for which there are no similar marketed devices to come to market, instead of having to submit a PMA. In 2009, it took an average of 770 total days to reach a *de novo* decision. **By 2014, we had reduced the total decision time by 66 percent.**



IDE. Manufacturers submit Investigational Device Exemptions (IDEs) for certain devices they want to study via a clinical trial. CDRH reviews an IDE submission before a manufacturer can begin to collect clinical data that may be necessary for future approval. **CDRH slashed median review times for IDE full approvals by more than a year between 2011 and 2015.**

Median Days to IDE Study Approval



DOING BUSINESS DIFFERENT

Since 2009, CDRH has been evaluating all of our programs to address concerns from patients, industry, health care providers, our own staff, and other customers about issues including review times, backlogs, and our expertise in increasingly complex technology. We have sought to address these concerns by **changing our culture** to put **patients first** and recognizing that **advancing innovation and assuring patient safety are not mutually exclusive**, revising or eliminating old policies, and developing new policies and approaches with an eye on meeting measurable objectives. Increased medical device user fees have supported these efforts so that we are better positioned to respond to the needs of patients.

- **Clinical Trials.** In addition to *dramatically improved performance*⁶ in reviewing IDEs, CDRH has encouraged the use of **innovative methodologies and study designs in clinical trials**. We recognize that manufacturers need CDRH input early and often so that the ultimate **device review process moves as quickly and smoothly as possible**. In 2013, CDRH issued final guidance for manufacturers on early feasibility studies to encourage conducting these studies in the United States. Innovators tend to market their technologies sooner in countries where they elect to conduct their early clinical studies. Since 2013, **the number of early feasibility studies approved has more than doubled—from 17 in fiscal year 2013 to 40 in fiscal year 2016**.

CDRH encourages the use of innovative clinical trial designs and statistical methods such as *adaptive clinical trials*⁷ and *Bayesian statistics*⁸ because, where appropriate to use, they can reduce the time and cost of a clinical study. In recent years, many devices have come to market based on the results of clinical trials using adaptive trial designs. **For the period from 2007 to May 2013, CDRH received 201 submissions that were adaptive.**

CDRH continues to develop computational models that can, in some instances, supplement or replace data from clinical investigations, such as the *Virtual Family (VF)*⁹—a set of highly detailed, anatomically correct, computational whole-body mod-

⁶ CDRH Clinical Trial Enterprise Targets and Performance.

⁷ Guidance Document: Adaptive Designs for Medical Device Clinical Studies Issued July 27, 2016.

⁸ Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials.

⁹ Virtual Family.

els, designed to mimic humans of both sexes at various stages of growth. **Since 2007, more than 160 submissions have included Virtual Family research.**

- **Flexible, Risk-Based Regulatory Approaches.** CDRH continues to adapt our oversight policies to emerging new technologies. In a manner consistent with our statutory mission, we now approach a medical technology by first asking whether active CDRH oversight will be value-added. If not, we take a less active regulatory approach. If it would, we focus on assuring timely patient access to technologies that will benefit patients by considering the device's innovation cycles and evidence generation needs.

For example, widespread adoption and use of digital health technologies is creating new and innovative ways to improve health and health care delivery. In **one of the biggest de-regulatory actions for CDRH in decades**, to foster greater innovation in the digital health space while promoting public health, we have exercised our enforcement discretion to cease subjecting certain lower risk medical devices (such as apps for patient care management and medication reminders) to medical device requirements.

Additionally, balancing data needs between what's collected before the device comes on the market (premarket) and what's collected after it is on the market (postmarket) reflects our approach to best assure timely patient access to safe and effective devices.

In 2015, CDRH completed a *retrospective review*¹⁰ of the benefit-risk profile of all types of high-risk devices to determine if we could reduce pre-market data collection requirements for at least some devices. As a result, for 30 percent of high-risk medical devices, **CDRH determined, based on the current body of evidence and experience, we could consider some devices candidates for down-classification, eliminate some data requirements or shift some pre-market data requirements to the postmarket setting.** In 2016, CDRH reached out to stakeholders for input on the results of the retrospective reviews, in order to determine next steps.

- **Patient-Centered Benefit-Risk.** For the past 5 years, CDRH has encouraged the use of a **more flexible, patient-centric, and transparent benefit-risk framework** to evaluate medical devices, starting with a 2012 guidance on the factors to consider when making benefit-risk determinations in support of device pre-market approval decisions, which includes patient perspectives on potential benefits and risks. We are focusing more on what matters to patients.

In 2016 and 2017, CDRH expanded this approach by revising the 2012 guidance to *include additional patient-centric factors*,¹¹ and issuing two additional benefit-risk guidance documents: one which outlines the principal factors CDRH considers when making benefit-risk determinations during the pre-market review process for *IDEs*¹², and one which outlines factors to consider when determining whether and what *postmarket actions*¹³ we may take to address a problem, such as a recall, based on the benefits and risks of that action to patients.

- **Patients as Partners.** CDRH had traditionally determined whether the benefits of a device outweighed its risks based on the tradeoffs we thought were acceptable. However, patients who live with a disease or condition often have their own perspectives on what benefits and risks related to medical devices they are willing to accept. CDRH collaborates with patient scientists and other experts outside the FDA to help us advance the scientific field of assessing patient preferences and incorporate the patient perspective into our benefit-risk assessments and decision-making.

For example, in 2014, CDRH funded a collaborative study on patient preferences that led to changes in our review paradigm for obesity devices, and used the results to inform our decision to approve the first medical device for treating obesity since 2007. Better understanding of patient preferences can also help **rejuvenate development pipelines**; since then, CDRH has approved or granted marketing applications for five more medical devices that address obesity or weight loss.

¹⁰CDRH Strategic Priorities and Updates.

¹¹Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and DeNova Classification (August, 24, 2016).

¹²Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Investigational Device Exemptions.

¹³Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Product Availability, Compliance, and Enforcement Decisions.

In 2016, CDRH issued a final guidance that outlined *patient preference information (PPI)*¹⁴ that CDRH may use in decisionmaking. Since then manufacturers have begun to submit—and we have approved—IDEs with patient preference studies.

CDRH's efforts to incorporate the voice of patients in our decisionmaking also are reflected in medical device clinical studies, which have been increasingly assessing what matters most to patients. Between 2009 and 2014, the number of **premarket submissions that included clinical studies with patient reported outcomes (PROs) increased by more than 500 percent** and half of IDE pivotal clinical studies now include PROs.

In 2015, CDRH established the first FDA advisory committee focused on the interests and needs of patients, and recruited potential new members in 2016. **The Patient Engagement Advisory Committee¹⁵ will hold its first meeting in 2017.**

- **National Evaluation System for Health Technology (NEST).** Despite rigorous premarket evaluation, we cannot fully understand how well a medical device works until it is used day-to-day by patients, caregivers, and clinicians. Premarket clinical trials provide critically important information but we don't understand the long-term benefit-risk profile until it is used in routine clinical practice. Currently our Nation is limited in its ability to make widespread use of real-world evidence (RWE) to best inform all members of the medical device ecosystem.

CDRH intends for NEST to increase the quality and use of real-world data (RWD) collected as part of routine clinical care, which should also help reduce the time and cost of evidence generation. Ongoing implementation of the Unique Device Identification (UDI) system also will enable NEST to perform enhanced analyses of devices on the market, providing a clear and standard way to identify devices in electronic medical records.

CDRH is already relying on RWE to approve new devices, expand the indications for already marketed devices, and reduce the time and cost for device makers to meet their postmarket study requirements. In 2016, CDRH documented access to more than 28 million electronic patient records (from national and international clinical registries, claims data, and electronic health records) that included device identification and awarded \$3 million to the Medical Device Innovation Consortium to establish the NEST Coordinating Center.

- **Streamlining the Pathway from FDA Approval to Payer Coverage.** Time-ly access to innovative medical technologies has been identified as a significant issue in the delivery of high quality health care. Manufacturers of innovative medical products have said that after undergoing the FDA approval process the availability of their products to consumers is often slow because, in order to obtain coverage and payment from third-party payers, the manufacturers must go through a second review process by such payers. Therefore, CDRH established the Payer Communication Task Force (PCTF) to facilitate communication between device manufacturers and payers to shorten the time between FDA approval or clearance and coverage decisions. By communicating earlier, manufacturers may design their pivotal clinical trials to produce both the data required for regulatory approval or clearance, and positive coverage determinations.

To support these efforts, CDRH and the Centers for Medicare & Medicaid Services (CMS) began to pilot an approach in 2011 called Parallel Review that would give eligible device makers the voluntary option for CMS to start their national coverage determination process while the device is under review by CDRH. This process serves the public interest by reducing the time between FDA marketing approval or clearance decisions and CMS national coverage determinations. In 2016, CDRH and CMS established Parallel Review as a permanent program. Last year, CDRH also established an additional opportunity for device manufacturers to invite CMS, private payers, or health technology assessment groups (HTAs) to join FDA pre-submission meetings to provide early feedback on clinical trial design.

EVIDENCE OF IMPACT

Our investments are starting to pay off. For example, in 2016, CDRH approved 91 novel medical devices—the highest number since the advent of the user fee program in 2003. This followed the second highest number from 2015, and continued a 7-year trend that has resulted in a marked increase in the annual number of novel device approvals since 2009. These novel technologies, which can help improve the quality of life of patients, especially those that require day-to-day mainte-

¹⁴Guidance Document: Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling.

¹⁵The Patient Engagement Advisory Committee.

nance and ongoing attention, are yielding promising results. In addition, several of these devices are reaching U.S. patients much earlier than they would have in previous years.

- **“Artificial Pancreas”** Approximately 5 percent of diabetics have Type 1 diabetes, also known as juvenile-onset diabetes. People with type 1 diabetes have to constantly monitor their glucose levels throughout the day and have insulin therapy through injection with a syringe, an insulin pen, or an insulin pump, to avoid becoming hyperglycemic (high glucose levels). Working interactively with the sponsor from the earliest stages of development to assist in making this technology available as quickly as possible while assuring it is safe and effective, **CDRH, in 2016, approved the first automated insulin delivery (AID) device in the world that is intended to automatically monitor glucose (sugar) and provide appropriate basal insulin doses—what some have called a first-generation “artificial pancreas.”**¹⁶

- **Transcatheter Aortic Valve Replacement (TAVR) Therapy.** About 80,000 surgical aortic valve replacements (SAVR) are performed in the United States annually. One-third of these patients are at intermediate surgical risk for death or complications. An aortic valve replacement that can be inserted through the blood vessels or, in some cases, through the tip of the heart by a catheter, rather than through open surgery, could avoid the risks of surgery and provide an alternative effective treatment to patients who are in the “intermediate surgical risk” category.

In 2011, CDRH approved the first TAVR device in the United States for patients who are not surgical candidates for SAVR, more than 4 years after the device entered the European Union (EU) market. When, in 2016, CDRH *approved the expanded indication*¹⁷ for use for a TAVR device in patients at intermediate surgical risk for death or complications, the positive impact of CDRH initiatives was evident. The gap between EU and U.S. approval for the expanded indication for use was reduced from over 4 years to only 18 days. U.S. Medicare coverage is also a factor in patients’ access to devices. For TAVR devices, access to real-world evidence—what NEST hopes to expand—proved to be a valuable asset. The U.S. Medicare program immediately covered TAVR devices due to the ongoing collection of real-world evidence on these devices in a national registry—there was no delay between U.S. approval and access to this technology. **As a result, more than 25,000 additional patients each year are now eligible for this life-saving procedure.**

- **Diagnostics for National Emergencies.** Accurate detection and diagnostics are critical to addressing national public health threats. For example, in 2016, CDRH authorized the use of 14 diagnostic tests for *Zika*¹⁸ virus under our Emergency Use Authorization (EUA) authority—12 tests to diagnose active infection and 2 tests to assess whether individuals who may have recently been exposed to *Zika* were actually infected. This rapid action provided timely patient access to *Zika* tests before the summer of 2016, when officials detected the virus in the United States. **Since 2009, CDRH has granted 50 EUAs, reauthorized 19 EUAs, and granted 30 amendments for tests to help meet the country’s needs during a national public health emergency, such as outbreaks from *Zika*, *Ebola*, and *H1N1*.**

Appendix B. Center for Devices and Radiological Health (CDRH)—2016–17 Strategic Priorities—2016 Accomplishments

ESTABLISH A NATIONAL EVALUATION SYSTEM FOR MEDICAL DEVICES

To successfully harness real-world evidence (“evidence from clinical experience”) in an efficient manner, the United States must develop the necessary infrastructure—a National Evaluation System for health Technology (NEST).

¹⁶The Artificial Pancreas Device System.

¹⁷ Press Release: FDA approves expanded indication for two transcatheter heart valves for patients at intermediate risk for death or complications associated with open-heart surgery—Aug. 2016.

¹⁸*Zika* Virus Response Updates from FDA.

Goal: Increase Access to Real-World Evidence to Support Regulatory Decisionmaking

| 2016 Target | Results |
|--|--|
| 25 Million. By December 31, 2016, gain access to 25 million electronic patient records (from national and international clinical registries, claims data, and EHRs) with device identification. | 28.6 Million. Gained access to more than 28 million electronic patient records (from national and international clinical registries, claims data, and EHRs) with device identification using a variety of mechanisms, such as cooperative agreements and access through regulatory process. |

Goal: Increase Access the Use of Real-World Evidence to Support Regulatory Decisionmaking

| 2016 Target | Results |
|---|--|
| 40 percent. By December 31, 2016, increase by 40 percent the number of pre-market and post-market regulatory decisions that leverage real-world evidence. (compared to fiscal year 2015 baseline). | 85 percent. The number of pre-market and post-market regulatory decisions that used real-world evidence increased by 85 percent in 2016. (compared to fiscal year 2015 baseline). |

Supporting Actions

In 2016, CDRH took a number of actions to achieve the goals and targets established for this priority:

- **Establish the National Evaluation System for health Technology (NEST).**

In Progress: A multi-stakeholder Planning Board and the Medical Device Registry Task Force issued a series of reports that outlined an organizational structure and infrastructure for the NEST Coordinating Center (*February 2015*,¹⁹ *April 2016*,²⁰ *September 2016*,²¹ *August 2015*,²² In 2016, FDA awarded \$3 million to the Medical Device Innovation Consortium (MDIC) to establish the Coordinating Center, and \$1 million to other organizations to continue projects that generate real-world evidence on device performance.

- **Develop a framework for the incorporation of real-world evidence into regulatory decisionmaking.**

In Progress: Issued *draft guidance*²³ to describe how real-world evidence may be used to support pre- and post-market regulatory decisions. Final guidance is planned for 2017.

PARTNER WITH PATIENTS

We believe that if CDRH is to successfully achieve a mission and vision in the service of patients, we must interact with patients as partners and work together to advance the development and evaluation of innovative devices, and monitor the performance of marketed devices.

Goal: Promote a Culture of Meaningful Patient Engagement by Facilitating CDRH Interaction with Patients

| 2016 Target | Results |
|--|--|
| 10 Organizations. By December 31, 2016, establish one or more new mechanisms for CDRH employees to obtain patient input on key pre- and post-market issues facing CDRH and foster participation of 10 patient groups. | 34 Organizations. CDRH staff participated in 21 patient interaction opportunities, involving 34 patient organizations. |
| 50 percent. By December 31, 2016, 50 percent of CDRH employees will interact with patients as part of their job duties. | 68 percent. More than 68 percent of CDRH interacted with patients in 2016. When asked, 99 percent of staff who interacted with patients described their interaction as meaningful and 89 percent as relevant to their jobs. |

¹⁹ Recommendations for a National Medical Device Evaluation System.

²⁰ The National Evaluation System for health Technology: Priorities for Effective Early Implementation; Planning Board Report.

²¹ The National Evaluation System for health Technology: Priorities for Effective Early Implementation; Planning Board Report.

²² Recommendations for a National Medical Device Evaluation System.

²³ Guidance Document: Use of Real-World Evidence to Support Regulatory Decisionmaking for Medical Devices.

Goal: Increase Use and Transparency of Patient Input as Evidence in Our Decisionmaking

| 2016 Target | Results |
|---|---|
| <p>50 percent. By September 30, 2016, 50 percent of PMA, <i>de novo</i> and HDE decisions will include a public summary of available and relevant patient perspective data considered.</p> <p>By September 30, 2017*, increase the number of patient perspective studies (e.g., evaluating patient reported outcomes (PRO) or patient preference information (PPI)) used in support of pre-market and post-market regulatory decisions. (Compared to fiscal year 2015 baseline).</p> | <p>65 percent. In fiscal year 2016, 65 percent of PMA, <i>de novo</i>, and HDE decisions included a public summary of available patient perspective data.</p> <p>65 percent. PRO and 4 PPI. Increased by 65 percent the number of approved IDEs (pivotal studies only) with patient reported outcomes (PRO). Increased to four (from none) the number of patient perspective studies conducted by sponsors in support of pre- and post-market regulatory decisions.</p> |

*2017 Target.

Supporting Actions

In 2016, CDRH took a number of actions to achieve the goals and targets established for this priority:

- **Patient Engagement Advisory Committee.** Convene the Patient Engagement Advisory Committee to discuss high priority topics regarding patient input in the total product lifecycle.

In Progress: CDRH chartered and began to recruit members for FDA's new Patient Engagement Advisory Committee (PEAC). PEAC members will be selected and announced in 2017.

- **Education and Training.** Develop education and training for CDRH staff and industry on the development and use of the science of measuring and communicating patient input throughout the total product lifecycle.

In Progress: CDRH trained more than 80 staff members on patient-reported outcomes (PRO) and patient-preference information (PPI), to advance staff understanding and CDRH review capacity in these areas.

PROMOTE A CULTURE OF QUALITY AND ORGANIZATIONAL EXCELLENCE

A manufacturer's ability to design and make high-quality, safe and effective devices and CDRH's ability to provide the necessary oversight to assure devices on the market are high-quality, safe and effective will increase as manufacturers and CDRH embrace a culture of quality and excellence throughout our respective organizations.

Goal: Strengthen FDA's Culture of Quality within the Center for Devices and Radiological Health

| 2016 Target | Results |
|--|--|
| <p>10 percent. By September 30, 2016, increase by 10 percent the number of CDRH staff with quality and process improvement credentials to improve organizational excellence. (compared to fiscal year 2015 baseline).</p> | <p>300 percent. In fiscal year 2016, CDRH tripled the number of staff with quality credentials by providing onsite quality training and certification examinations.</p> |

Goal: Strengthen Product and Manufacturing Quality within the Medical Device Ecosystem

| 2016 Target | Results |
|---|--|
| <p>By September 30, 2016, develop metrics, successful industry practices, standards, and tools that manufacturers can use to evaluate product and manufacturing quality beyond compliance with regulatory requirements.</p> <p>By December 31, 2016, pilot voluntary use of product and manufacturing quality metrics and evaluation tools.</p> | <p>Partnered with MDIC to develop metrics and best practices to assess quality system performance, and analytical tools to assess device quality by hospital value analysis committees.</p> <p>Partnered with MDIC and Capability Maturity Model Integration (CMMI) Institute on a proof-of-concept and pilot with three device manufacturers, to evaluate use of the CMMI appraisal process as a foundation for a future third-party program.</p> |

Supporting Actions

In 2016, CDRH took a number of actions to achieve the goals and targets established for this priority:

- **Quality Management Framework.** Resources permitting, continue to implement the CDRH Quality Management Framework.

In Progress: CDRH completed development of its document control system (DCS). DCS will ensure that current and approved quality program and key processes documentation—standard operating procedures, work instructions, forms, templates and process maps—is available to staff.

- **Education and Training.** Develop education and training for CDRH staff to facilitate adoption of practices characteristic of a culture of quality and organizational excellence.

In Progress: CDRH became an American Society for Quality (ASQ) enterprise member—enabling every employee at FDA to take advantage of ASQ’s vast collection of learning resources. CDRH also offered onsite quality training to 150 staff. More than 90 percent of those who participated in the training earned ASQ quality certifications (Certified Quality Auditor and Certified Quality Improvement Associate).

- **Case for Quality.** As part of the Case for Quality, collaborate with members of the medical device ecosystem to identify, develop, and pilot metrics, successful practices, standards, and evaluation tools that will be specific to the medical device industry and focus on assuring product and manufacturing quality.

In Progress: In partnership with MDIC, CDRH collected input from stakeholders through six Case for Quality Forums; developed metrics and best practices designed to assess quality system performance using pre-production, production and post-production data; and led development of a product quality dashboard to assist hospital-value analysis committees in identifying high quality devices.

- **Voluntary Program.** Identify external partnerships and mechanisms to support a sustainable, voluntary third-party program that will utilize quality metrics, practices, standards, and evaluation tools to assess and promote medical device product and manufacturing quality within industry beyond compliance with regulatory requirements.

In Progress: Continuing partnership with MDIC, CMMI Institute and other stakeholders, to expand application of maturity appraisal process; with the goal of developing the framework for a voluntary program in 2017.

Appendix C. BsUFA Meeting Types

The BsUFA program established five meeting types specific to biosimilar development programs:

- A Biosimilar Initial Advisory meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service (PHS) Act may be feasible for a particular product.

- A BPD Type 1 meeting is a meeting that is necessary for an otherwise stalled BPD program to proceed. Examples of a BPD Type 1 meeting include discussion of: a clinical hold, a special protocol assessment, an important safety issue, dispute resolution, and/or a Complete Response.

- A BPD Type 2 meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing BPD program. This meeting type includes substantive review of summary data, but does not include review of full study reports.

- A BPD Type 3 meeting is an in-depth data review and advice meeting regarding an ongoing BPD program. This meeting type includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding the need for additional studies, including design and analysis. This meeting has no counterpart in the Prescription Drug User Fee Act (PDUFA) program and is unique to BsUFA to support an evaluation of residual uncertainty regarding the demonstration of bio-similarity and to support the concept of stepwise evidence development.

- A BPD Type 4 meeting is a meeting to discuss the format and content of a biosimilar biological product application or supplement to be submitted under section 351(k) of the PHS Act.

The CHAIRMAN. Thank you, Dr. Woodcock.
Dr. Marks.

STATEMENT OF PETER MARKS, M.D., Ph.D., DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. MARKS. Mr. Chairman and members of the committee. Thank you for the opportunity to provide this testimony today on the reauthorization of FDA's User Fee Acts.

At the Center for Biologics Evaluation and Research, we have regulatory responsibility for many complex biologics including vaccines, allergenic products, blood and blood derivatives, and cellular tissue and gene therapies.

As part of this responsibility, in addition to biologics, we also regulate medical devices used to prepare blood and tissue products, and blood and tissue screening tests to prevent infectious disease transmission.

The unique products that we regulate range from vaccines, which are administered routinely to almost all Americans to protect the public health, to gene and cellular therapies that are on the cutting edge of science and show promise for the treatment of seriously ill patients including those with rare disorders.

These User Fees play an important role in supporting our review of many of these critical products, promoting innovation, and speeding the availability of medical products to those who need them.

Though we regulate a wide variety of products, a common theme that runs through all of our complex biologics is that their safety and efficacy are intimately intertwined with the quality of their manufacturing processes. Indeed, some of the products that we oversee involve the most complicated and advanced technologies in pharmaceutical manufacturing.

Just one illustration of this is the pneumococcal conjugate vaccine, which involves 14 different fermentation processes and 39 chemical reactions for production.

Indeed, vaccines represent one of the most important public health measures widely implemented during the 20th century that resulted in a significant decrease in morbidity and mortality in both children and adults. Vaccines are still every bit as important in the 21st century for maintaining public health.

The correlation of the introduction of infective vaccination campaigns in the United States with the elimination of polio virus is incontrovertible and there are similar data for other infectious diseases.

Our Center plays a key role in ensuring the safety, effectiveness, and availability of our Nation's vaccines. For example, in collaboration with other Federal partners, the Center plays an integral role in national and global preparedness for seasonal and pandemic influenza.

In addition to licensing vaccines, we are involved across the vaccine development process from influenza virus strain selection, to preparation of crucial reagents in our laboratories for distribution to manufacturers, to monitoring large databases like the Sentinel System to ensure the post-marketing safety of the vaccines that we approve.

CBER also regulates some of the most highly innovative biologic products that have the potential to transform medical care. These

include gene therapies and genetically modified cellular therapy such as chimeric antigen receptor T cells.

Although there is not yet an approved gene therapy, such therapies very much appear to be on the horizon. In fact, the Center currently has 560 active investigation new drug applications involving gene therapy while having received 82 applications in 2016 alone.

Given the thousands of rare diseases without effective or optimal therapies available, it is relevant to note that more than two-thirds of these applications address such rare diseases, which include both inherited conditions and acquired diseases such as certain cancers.

Toward the objective of further expediting the development and approval of important cellular and tissue-based therapies addressing unmet medical needs and serious and life-threatening conditions, the Center is very actively working to implement the Regenerative Medicine provisions of the 21st Century Cures Act that Congress recently enacted.

We are now receiving requests for Regenerative Medicine Advanced Therapy, or RMAT, designation and our Center looks forward to working with sponsors of these products along with other stakeholders in order to help facilitate the availability of those new therapies to patients.

Because of the broad scope of the products that we regulate, which even include a few generic drugs, our Center is supported in part by all four of the existing Medical Product User Fees. User Fees fund approximately 44 percent of the full time equivalents at the Center. The agreements that have been reached and the resources that they have provided the Center, along with the rest of the agency, have resulted in reduced time to regulatory actions.

For example, during the past 5 years, we have met or exceeded the performance goals regarding product reviews for both the Prescription Drug and Medical Device User Fee Agreements of 2012. A number of our performance measures have improved significantly.

In addition, User Fees have helped make it possible for us to fully implement recent initiatives that facilitate product development, such as the Breakthrough Therapy designation that was enacted by Congress in 2012. In this regard, as of January 31, 2017 our Center has received 93 breakthrough designation requests and we granted 27 of those requests.

The support from User Fees is a critical factor in providing us with the resources for the accomplishment of our Center's mission to protect and promote the public health by expediting the development and approval of important and innovative medical products.

We greatly appreciate your efforts toward ensuring the seamless continuation of the User Fee Agreements that have helped facilitate the availability of such products for the benefit of the health of the people of our Nation.

Thank you once again for the opportunity to provide this testimony.

I look forward to answering any questions that you might have.

The CHAIRMAN. Thank you, Dr. Marks.

Dr. Shuren. Welcome.

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

Dr. SHUREN. Thank you, Chairman Alexander, Ranking Member Murray, members of the committee.

Thank you for the opportunity to have me here today to discuss the reauthorization of the Medical Device User Fee Amendment or MDUFA.

When I was last here testifying about MDUFA, I am sure many of you may recall that the program was in a much different place. Since then, much has changed for the better, but we have more work to do.

Between 2010 and 2016, we reduced the average total time to reach a decision on the 510(k)—the submission type required for low to moderate risk devices—by 11 percent.

Between 2009 and last year, we reduced the average total time to reach a decision on the PMA—the submission type required for the highest risk devices—by almost 150 days, a 35 percent decrease.

We went beyond our MDUFA III commitments. For example, we reduced the median time to approve a clinical trial submission from 442 days in 2011 to just 30 days in 2015 and 2016, a 93 percent decrease.

Changes we have made at the Center for Devices and Radiological Health, or CDRH, to our culture, policies, and processes, the investment provided by industry through User Fee funding, and the direction provided by Congress through changes to Federal law have resulted in an improved medical device pipeline and innovative technologies being introduced into the United States earlier than in the past.

In fact, the number of novel devices we have approved has almost quadrupled from 24 in 2009 to 91 in 2016, the highest since the advent of the Medical Device User Fee program in 2003.

In fact last year, we approved the first artificial pancreas working interactively with the device manufacturer from the early stages in development.

FDA approved the first device in the world that is intended to automatically monitor glucose levels around the clock and automatically provide appropriate insulin doses. Overall, working with the manufacturer, we helped bring this technology to market 3 years earlier than the company had originally planned.

MDUFA IV could continue the trajectory of more timely patient access to novel technologies, supporting CDRH's vision that patients in the United States have access to high quality, safe, and effective medical devices of public health importance first in the world.

The MDUFA IV proposal submitted to Congress in January includes programmatic enhancements, such as a new quality management program that will improve consistency, efficiency, predictability, and the application of the least burdensome approach in our premarket review program and decisionmaking.

The proposal would also allow the FDA to move forward in some critical and strategic areas, such as strengthening our partnerships with patients, allowing us to promote more patient-centric clinical

trials, advanced benefit risk assessments that are informed by patient perspectives, and foster earlier patient access to new devices.

Another critical area is the development of the National Evaluation System for health, with a small “h,” Technology or NEST. The NEST is a nongovernment system that will be operated by stakeholders of the medical device ecosystem including patients, providers, and the medical device industry. That would facilitate the use of real world data collected as part of routine clinical care, such as from electronic health records and registries consistent with the goals of 21st Century Cures.

A robust NEST will enable manufacturers to harness real world evidence that could enable them to drive down the time and cost to bring a new device to market, expanding indications for already approved devices, meeting post-market reporting requirements, and obtaining payer coverage and reimbursement.

The NEST will also enable faster identification of safety issues, reducing harm to patients and liability for companies.

In conclusion, reauthorization of the Medical Device User Fee program could expedite the availability of innovative new products, create jobs, protect patients, and provide the enhancements that will continue to increase the efficiency of FDA’s programs.

Improvements in total time to decision, transparency, consistency, predictability, efficiency, and assuring the least burdensome approach will benefit industry, healthcare providers, and most importantly, patients.

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

The CHAIRMAN. Thank you, Dr. Shuren.

We will now have a 5-minute round of questions. I am going to defer my questions, and we will start with Senator Burr, and go to Senator Murray.

STATEMENT OF SENATOR BURR

Senator BURR. Thank you, Mr. Chairman. Thank you for holding this hearing.

I welcome our agency folks from the FDA. Let me ask all of you, if I can; just a yes or no answer.

Would you be opposed to a modification in the Agreement that would return a percentage of the User Fee money to any manufacturer for those portions of the Agreement you did not live up to? Yes or no.

Dr. Woodcock.

Dr. WOODCOCK. Yes.

Senator BURR. Yes?

Dr. WOODCOCK. Yes.

Senator BURR. Dr. Marks.

Dr. MARKS. Yes.

Senator BURR. Dr. Shuren.

Dr. SHUREN. Yes.

Senator BURR. OK. Listen, as a part of the 2012 PDUFA, the FDA promised to hire an additional 129 employees to review applications and to conduct other critical tasks to improve the performance of the agency.

For the 2013 through 2017 cycle, the agency has only hired 86 percent of the total number of new, full-time paid for by the industry. So the FDA has not been able to hire all the employees agreed to under the PDUFA agreement.

Does the agency plan to return those dollars?

Dr. WOODCOCK. No.

Senator BURR. Do you feel that living up to the agreement that you made with the industry is important?

Dr. WOODCOCK. Absolutely.

Senator BURR. Has the FDA ever diverted User Fee money to construct buildings versus to hiring employees as was part of the agreement?

Dr. WOODCOCK. To my knowledge, the agency has only spent money on the User Fee Agreements for the things that are allowable under there. Certainly, rent and overhead costs are one of the allowable costs.

Senator BURR. The White Oaks Facility did not take User Fee money for construction?

Dr. WOODCOCK. I do not know the answer to that. We can get back to you.

Senator BURR. I would love for you to. I think that User Fees, dollars toward rental payments totaled \$59.54 in 2015, that is GAO. Let me say, 27.1 of that was devoted to staff and it went toward rent.

Listen, this is really important. I believe all the statistics as you have told me. I have heard them for 23 years from the FDA.

Let me ask this, has what you agreed to in the User Fee Agreements differed greatly from the 1997 statutory requirements that you had?

Dr. WOODCOCK. For drugs, there has been significant difference in the amount of advice we give.

Since the first User Fee program, which set timeframes for conducting the premarket review, much of the attention has been paid to providing advice to industry in meetings during drug development and developing standards. Because the most important thing for the drug industry, at least, is predictability; so what is needed to get it onto the market? What standards have to be met?

Senator BURR. I believe we negotiated that in the last Agreement.

In 2015, FDA did not meet five of the meeting management goals established under the User Fee Agreement. A critical piece of the review process is the communication between the agency and the sponsor of the drugs, biologics, or devices.

Regular correspondent progress updates, meetings between the two parties create greater predictability and certainty throughout the process. The agency promised to schedule 80 percent of certain meetings within 75 days. That is over 2 months allowing for a meeting to be set up.

The agency scheduled only 49 percent of these meetings. You came up short of what the goal was in PDUFA, yet there is in this Agreement no penalty that the FDA pays.

If you do not meet the FTE's that you agreed to in the agreement, there is no penalty that the FDA meets.

If money is diverted over to rent versus to processing applications, there is no penalty that is met.

Ninety-two percent of priority applications are approved in the first review cycle at the FDA and now, this is great news. However, that is not the case for standard applications moving through the agency. The percentage of standard applications approved in the first review cycle is 60 percent.

What is the reason?

Dr. WOODCOCK. The reason, generally, is that more questions arise. Standard applications do not provide an additional health benefit to the public. They are usually another option. The burden on them to be at least as good as what is out there is somewhat higher than something that is curing something.

Senator BURR. Could that be part of 51 percent that did not get a regularly scheduled meeting?

Dr. WOODCOCK. That I cannot comment on.

Senator BURR. Let me just ask you, my time is running out.

Dr. WOODCOCK. I would like to, if I may, explain that rent is an allowable part of the User Fee Agreements, as I said earlier.

Senator BURR. Well, I just want my colleagues to be fully aware of what User Fees go to. They do not necessarily go to put reviewers in front of applications to make decisions that live within the timeframes that you agreed to.

Since we are new to Generic User Fees, how has the backlog changed on generics in this first User Fee period?

Dr. WOODCOCK. Prior to enactment of the first Generic User Fee program, there was a very large number of applications, thousands, sitting at the FDA that had not been picked up and looked at.

Typically before that program started, they would go through a minimum of four cycles of review before they got out onto the market and done, which meant some of them went through 11 cycles of review.

We have reviewed virtually all of those applications. They have been reviewed and many of them—there are 1,800 current applications sitting back with the manufacturers waiting for them to decide whether to resubmit them or move on.

We have 2,300 applications in process at the FDA, under review, with goal dates. So they have a predictable path that they will follow.

I cannot tell you at the end of their review that every one will get approved. Why? Some of them have manufacturing facilities that are unacceptable and we cannot approve generics where the parties have, perhaps, made up data or other things. So there may be blocks. We will send them a complete response saying, "You have to fix this problem."

However, everything is under goal right now and it is a predictable process for the industry. Not as fast as they would like it to be, or we would like it to be, because we had to get through that huge bolus, which I compared to like a python trying to, or a snake, trying to swallow a giant donkey or something like that. It was an amazing amount of work that we had to get done, but it is in process.

Senator BURR. We need to move on.

The CHAIRMAN. Thank you, Senator Burr.

Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman.

Before I ask my questions, I do have to say again, I am deeply concerned that we have a major healthcare bill moving through Congress that has not had a hearing.

As a reminder, during consideration of the Affordable Care Act, this HELP committee held 47 bipartisan meetings on that issue including 14 bipartisan roundtables, 13 bipartisan hearings, and 20 bipartisan walk-throughs.

It is really concerning to me that given all of the harm and chaos and everything that goes along with Trump Care, there are no plans in this committee to talk about this legislation as it moves through. I have a lot of constituents, like I am sure many of us do, coming up to us with really personal stories. They are very fearful and I just think it is critical that this committee have a hearing to talk about the impact of this legislation.

I hope our colleagues think about why they do not want to have a hearing and hope they agree to allow us to have some closer scrutiny of this. I think it is extremely critical and I am going to stay focused on it.

On this subject, Dr. Woodcock, let me talk with you first.

Polls show that the high price of prescription drugs is one of America's top health concerns. We know when costs are too high, patients sometimes forego their necessary treatments.

However, the FDA is not permitted, of course, to set drug prices. I am hopeful that our Republican colleagues will work with me and other Democrats on this side of the aisle. CMS is currently prohibited from negotiating the price of drugs under Medicare Part D. I would love to work on reviewing that, seeing if we can change that.

The FDA can help promote a robust, competitive marketplace that makes treatments more affordable for patients by continuing to advance generic and biosimilar drugs.

Dr. Woodcock, can you tell us the key ways the generic and biosimilar agreements will help to get those products to market for consumers?

Dr. WOODCOCK. In the generic space, it is very important that they not only have a predictable process, we also need to shorten the cycle numbers.

Having four cycles as happened in the past is an inefficient process for both the industry and the FDA. It wastes resources. We would like to move to where we have finally moved in the Prescription Drug User Fee program where the majority of approvals are after one review cycle. That is No. 1; a predictable, prompt path to the market.

Other parts of the Agreement include us continuing research. There are parts of the innovator, the brand drugs, certain types of products that really have very little generic competition. That is because you cannot do traditional bio-equivalents testing on them. For example, topical drugs and drugs with other routes of administration other than oral.

We have been doing research on these and have begun to develop methods whereby instead of doing large clinical trials to get a generic on the market, which is, of course, counterintuitive that we

can use other methods to show they are just the same as the innovator.

Similarly in the biosimilar world, the advanced methodology that we have is helping us compare the drugs before they go into any clinical testing in the biosimilar world, and this is what is allowing biosimilar development.

These activities are really helping enhance competition.

Senator MURRAY. According to the FDA's own data, there are over 2,300 applications for generic drugs in some stage of the review process at the FDA.

How many of those 2,300 applications are for products that would offer competition to a brand name drug for the first time or products that could bring competition to an uncompetitive market; the kinds of products that could actually bring new competition to some of the high-priced drugs?

Dr. WOODCOCK. My understanding is there are six waiting, but they have to wait, offer experience, and so forth. Six first generics and there are nine where they are a sole source, where there is only one other. Is that correct, Keith? Yes, that is correct.

Senator MURRAY. That is not very many.

Dr. WOODCOCK. That does not address the entire problem.

I must stress that the second Generic Drug User Fee program has many features that is intended to move these along as much as possible. We have a preprogram, as I said, for complex generics, which is an area where there is difficulty getting generics on the market, where we give advice and more handholding on how to get through the process for these more complicated products.

We also have, right now, a prioritization program where first generics and sole source products can be expedited in their review.

Senator MURRAY. Well, I appreciate it. It is not very many.

Dr. WOODCOCK. No.

Senator MURRAY. I think it is pretty clear that this agreement will make some important improvements to the generic drug approval process, which I support. But it alone is not going to solve the drug crisis. We are going to have to work outside of this to make that happen.

Thank you.

The CHAIRMAN. Thank you, Senator Murray.

Senator Collins.

STATEMENT OF SENATOR COLLINS

Senator COLLINS. Thank you, Mr. Chairman.

First, let me thank you for holding this hearing. We are facing the expiration date of September 30 for four laws that authorize these extraordinarily important fee programs that have helped to improve the healthcare, and the availability of medications and devices for the American people. I am glad that you are moving ahead and not jeopardizing these programs.

Speaking of which, Dr. Shuren, I was delighted to hear you talk about the artificial pancreas. I chaired and founded the Diabetes Caucus in the Senate back in 1998. We have tripled funding for research, which has helped.

The collaboration that you talked about that has allowed the artificial pancreas to come to market 3 years earlier, I believe you

said, than otherwise would be the case is going to make such a tremendous difference in the lives of so many children who have Type 1 diabetes.

I remember holding a hearing on the promise of an artificial pancreas 10 years ago, and it was really wonderful to learn of this development last year, and to see it coming to market.

I understand, however, that the initial access is going to be limited to older children and adults with Type 1 diabetes.

Can you update me on what is going on as far as clinical trials to allow younger children access to this potentially life altering technology?

Dr. SHUREN. I appreciate, by the way, all your support in the diabetes community for all these many years.

So yes, the device will be available for patients, really, 14 and older, but additional data is being collected in terms of younger children. The reason is because they are more active; their lifestyle is different. We just have to make sure that that technology, that they are able to use it given how they eat, how they play. But it is our hope that that will move forward very quickly as well.

Senator COLLINS. Thank you. That is great news.

Dr. Woodcock, as you are well aware, the Senate Aging Committee, which I chair, spent a whole year looking at the explosion in prices of off-patent drugs for which there was no generic equivalent.

One of the issues that we identified were the restricted distribution programs that were intended to prevent side effects, or they were high-risk drugs that patients were going to be using. So they were intended to be pro-consumer.

What we found is that these systems could be abused to delay generic entry into the marketplace. And the abuses are serious. By one estimate in 2014, such abuses resulted in increased costs to consumers of \$5.4 billion per year.

We have talked before about the REMS system that has been used by some drug companies to prevent potential generic competitors from getting access to the drugs, so that they can conduct the bioequivalent studies that you require.

What can be done to ensure that these restricted distribution programs, which were enacted with the best of intentions, are not abused and are a source of delay for generics coming to the marketplace?

Dr. WOODCOCK. These are a source of delay in two ways.

No. 1, as you said, companies are refusing to give drugs to the generic companies so they can perform the bioequivalent studies.

We have done a program to try and counter that. We review the protocols of the generic company, the clinical bio-equivalents protocol, and then we send a letter to the innovator company saying, "We find this acceptable. There are no problems." But we cannot force brand companies to give a drug to generic companies.

We do talk to the FTC. We send them information when this happens, and we have actually sent about 150 different settings about drugs over to them regarding this.

REMS are also a source when there is a restricted distribution system and Congress had said in the original FDA Amendments Act that there had to be a single shared system unless there were

good reasons not to, which means the innovator would have to have a shared system of distribution with its competitors.

This has delayed availability of generics a very long time, in some cases, and that is something we cannot do too much about. That is a standing law on the books. It says there should be a single shared system.

In some cases, we have had to go to separate systems that talk to each other so that the generics actually can come onto the market.

Senator COLLINS. So, would you like to see a change in the law in that area?

Dr. WOODCOCK. Well, I cannot comment on that, but I would say that that is a problem that we are seeing.

Senator COLLINS. Thank you, Mr. Chairman. I hope when we get to the markup stage, that the bill that Senator Claire McCaskill and I introduced as a result of the investigation we did in the Aging Committee will be part of our consideration.

The CHAIRMAN. Thank you, Senator Collins.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman.

I am grateful for you holding this hearing.

I want to also join Senator Murray and just urge my colleagues to find a way to have a bipartisan discussion as this healthcare bill comes forward.

I did 2 days of town meetings last week all over Colorado in Democratic and Republican areas. There are a lot of people, as everybody on this panel knows, who are dissatisfied with our healthcare system right now as it is, and they are worried that the Congress is about to make it even worse than it is.

Sign me up. We had 13 hearings here. We had a 7-day markup in the Finance Committee. We had, I think, 25 days on the bill in the Senate, and I remember some people saying it was being rushed through even with that kind of approach. I hope we can work to improve something as it comes through.

Second, I would like to thank Senator Collins for her leadership on diabetes and also recognize the good work that Dr. Shuren and his team have done.

I had Commissioner Califf out to Denver to visit the Barbara Davis Center and to meet a number of young people there who are just so excited about the potential of this artificial pancreas to change their lives. And there is more work, obviously, to be done there.

It is just a reminder that the work you do, and the work we do, can actually improve people's lives and that people are watching. And not withstanding the politics around here, they would like their government to actually be responsive to them. I want to thank you also for the progress that you have made in terms of the speeding up of approvals of medical devices.

You mentioned, Dr. Woodcock, the Breakthrough Therapies legislation that Senators Burr, and Hatch, and I wrote a number of years later. We now have seen that about 50 drugs have been approved as a result of that legislation. Treatments such as Kalydeco

for cystic fibrosis have made a dramatic difference in the lives of Coloradoans who are fighting a life or death disease.

I would love to hear you talk a little bit more about why you think that has been a success? What we have learned from that that we are going to be able to apply in other parts of the agency, if others would like to be responsive?

A question also is that when we look at the Breakthrough Therapies, only one has been approved for use in a neurological disease, specifically Parkinson's and I wonder whether you could address Coloradoans who are suffering from ALS, Alzheimer's, and other neurological diseases? How we can better support efforts to identify and speed up the approval of promising new therapies for neurological?

Maybe we will start with Dr. Woodcock and then if anybody else wants to respond.

Dr. WOODCOCK. Well, the Breakthrough Therapy program has put focused attention on potentially game-changing drugs. And we have been lucky that there are more of them now, probably because of the advance of science.

When we get that preliminary clinical data—as you said in the statute that shows that promise to be a game changer—we focus management attention on that development program, make sure it is as streamlined as possible, and we really help the sponsors get over the finish line for those drugs. That is really a very important intervention that has led to this.

As far as neurologic diseases, we did recently approve a very high-tech product called Nusinersen for spinal muscular atrophy, a fatal disease of children and a debilitating disease of young people. That was approved to slow down the disease and it is actually an antisense oligonucleotide.

Senator BENNET. Hold on. Let me write that down.

Dr. WOODCOCK. Yes, it probably takes more than 5 minutes to explain, but it is a very high-tech intervention that actually turns on a gene and helps produce the protein that is missing and is needed.

We are starting to see that, but neurologic diseases are behind cancer and other diseases. We do not know as much about them.

As I said many years ago to someone on this committee, that if we had put a war on neurologic diseases at the same time we declared a war on cancer, we probably would not be having this conversation. But our scientific understanding of neurologic diseases has lagged. But the good news is we have a robust pipeline now.

Senator BENNET. Is there anybody else who would like to?

Dr. Marks.

Dr. MARKS. I would just quickly add that I think that for our products too, we are starting to see products for neurologic diseases start to come into our Center. The Breakthrough designation is something that, with the enhanced communication, hopefully as those products come down the pipeline, we will help bring those forward more quickly to patients.

Senator BENNET. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Bennet.

Senator Young.

STATEMENT OF SENATOR YOUNG

Senator YOUNG. Thank you, Mr. Chairman, for holding this important hearing.

I want to thank the Ranking Member for her support of this hearing as well, and thank our panelists.

Regenerative medicine has been invoked a number of times here. I think it is really exciting the possibilities in that area and I thank you for your work there. It provides hope to those whose family members die on account of a lack of sufficient supply of organs being available in this country.

I just want to publicly announce my interest in this issue. There is no organized constituency, to my knowledge, of family members of people awaiting organ donations in this country. We have, I think to put it mildly, a suboptimal system, and I am looking for opportunities to make improvements there.

Turning to User Fees, the pharmaceutical and medical device industries are very important to the State of Indiana, not just on account of the jobs that they lead to, but we are proud of the innovations in the area.

The 21st Century Cures Act and the Prescription Drug User Fee Act VI—the technical agreement—directs the FDA to explore uses of real world evidence that are now possible. We can pull a raft of evidence out of clinical trials and analyze that to assist our regulatory decisionmaking. We directed that that be done in furtherance of safety and effectiveness.

How will the FDA approach the exploration of this new area of regulatory science? And does the FDA have some plans to learn from the experiences of other sectors, say, the health insurance sector, various hospital systems, and their use of real world evidence with regards to reliance on real world evidence?

Dr. WOODCOCK. Well, certainly we have harnessed the health insurance industry data. Our Sentinel System has about 193 million patient experiences and different patients from claims data from health insurance. That links to what happened to them, what their diagnosis was, what condition they were hospitalized for.

We have used that many times. That is now part of our routine safety, surveillance, and assessment of signals that we get on safety. We can go into those data, and do analyses, and bolster the evidence, whether there is a real safety problem or whether it was simply something that was a false signal.

Senator YOUNG. So you are looking at claims data in those data packages FDA receives.

Any other sort of data sets from registries?

Dr. WOODCOCK. Absolutely. We are interested in data in any possible form we can get it. We do work with, say, PCORnet. They have set up a network that includes the electronic health record, and we are very interested in integrating that into Sentinel. We do this work with the Center for Biologics.

That will take some more work, but we are working on that integration, and getting all the standards together, and so forth. We want to incorporate registries. I know devices, maybe Jeff, you ought to talk about that more.

Dr. SHUREN. Yes. We are already using device registries, and we have been involved in helping to set up over two dozen device registries.

In the past 6 years, we have been engaged in over 50 projects related to real world evidence. We are currently relying on it to approve new devices. Last year, we approved a balloon catheter based upon registry data.

We are expanding labeling indications based on it. In fact, in one case for a heart valve, the company was going to do a clinical trial. We saw the data was good enough in registry. We called the company and said, "Do not do the study. Send us a request. We are going to approve the indication."

We are using it for post-market studies. We are finding nesting clinical trials in a registry is reducing costs by about 40 to 60 percent.

Senator YOUNG. Fantastic. Moving to MDUFA, or the Medical Device User Fee Act IV. That Agreement includes new requirements for User Fee revenue to support the National Evaluation for health Technology to develop a coordinating center with expertise in the use of real world evidence to support premarket activities. A number of pilot projects are to be created.

Could you very briefly discuss how these are going to work and how they might allow patients to benefit from new safe and effective technologies more quickly?

Dr. SHUREN. Well, first off, this is not a Government system, so we have already provided initial seed funding to the Medical Device Innovation Consortium, a public-private partnership, to serve as the coordinating center.

They are in the midst of hiring an executive director and setting up a governing committee that has representatives from the device ecosystem. So patients will also have a voice in that entity.

As part of the pilots, they are going to be looking at return on investment for use of real world evidence in approving products, expanding labeling indications, and using it for malfunction summaries.

Also as part of it, they will start laying out the rules of the road, infrastructure and methodologies, to make greater use. The whole goal here is drive down the time and cost, and increase the value of use of real world data.

Today, there are a lot of challenges in using the data. It may be of poor quality or incomplete. The other is, it is only available for certain devices. We want to make that available more systematically across the device industry.

Senator YOUNG. Thank you.

The CHAIRMAN. Thanks, Senator Young.

Senator Murphy.

STATEMENT OF SENATOR MURPHY

Senator MURPHY. Thank you, Mr. Chairman.

I just think it is outrageous that we are holding this hearing today instead of talking about what is actually happening in this building right now; an effort to rewrite the rules that concern one-sixth of this country's economy.

An effort to jam down the throats of the House and the Senate the repeal of the Affordable Care Act, the most massive change in American healthcare in our entire lifetime. We are not talking about it in the Health Committee. We are the Health Committee. We are charged with overseeing the American healthcare system. And we are acting as if this is not happening.

IPDUFA, MDUFA, I understand they are important, but I am just going to tell you, the people that are sitting in this audience today, they are not representing uninsured Americans. They are representing the industry by and large. They are representing the million and billion dollar companies that have a lot at stake in this legislation.

We are the Health Committee and I do not know what the relevance of sitting on this committee is if we have nothing to do or say about a piece of legislation that is going to dramatically alter the landscape of American healthcare for our constituents.

We have heard about what the Health Committee has done in the past, and so, I will not regurgitate those numbers, but I watched those hearings. I was proud to watch those hearings.

In the Health Committee, there were 300 amendments that were considered in developing the ACA. There were 160 Republican amendments that were accepted as part of that legislation. Republicans did not vote for it in the end, but this committee had the chance to weigh in. The American people got to see over the course of a year an actual debate play out.

And though Republicans eviscerated Democrats for ramming that bill through, let us be honest about why we are not having a hearing here today. It is because my Republican colleagues did not learn a lesson of a bill being rammed through the process. They actually think that process took too long.

The reason that this bill is being jammed through on an extraordinary timeframe is because the lesson they learned from the ACA is that there was too much debate, and so they want less so that nobody can see what is in this bill.

I get that we can make your job easier and speed more transformational drugs to market, but if you do not have insurance to afford these drugs, then nothing we do here in the reform of these User Fee Agreements matters.

Twenty-four million people are about to lose their healthcare. That is the entire population of Alaska, Delaware, Hawaii, Idaho, Kansas, Maine, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Rhode Island, South Dakota, Vermont, West Virginia, and Wyoming.

This is not a minor adjustment of the number of people who have access to the drugs that we are talking about here today. This is a humanitarian catastrophe that is about to happen, and we are pretending like the debate does not exist.

I asked to be on this committee because I wanted to be at the center of the most important debates about the future of the American healthcare system. But it is possible that next week in the U.S. Senate, we are going to be asked in a handful of hours to vote up or down on a bill that is going to dramatically change the reality of healthcare for consumers all across this country. Driving rates up for millions of people, especially older Americans, taking

healthcare away for millions of Americans, passing on enormous tax breaks to the drug industries that we are talking about here today to healthcare insurance companies. This committee will have nothing to say about it.

I do not have any questions for the witnesses.

The CHAIRMAN. Senator Roberts.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Well, thank you, Mr. Chairman.

Back to the subject at hand.

Thanks to the panel. I am pleased to see the increased reporting, more timelines, stronger commitments to patient engagement, and independent third-party reviews.

With the combined 30 percent increase for fees proposed for next year, as Senator Burr so aptly described, that is over 100 percent for the biosimilars alone. I hope you are all prepared for the increased workload which will be required to turn this investment into increased and improved treatment options for the patients.

We certainly, here on the committee, do not want to slow down approvals as these are important therapies to get on the market. We have heard a lot of frustration and confusion with how to proceed in their absence.

I appreciate that in the commitment letter that you gave us, there are specific timelines laid out on the interchangeability. Your agreement states that the FDA will publish draft guidance by the end of this year, and finalize within 24 months after the close of the comment period. That puts us into 2020. That is 10 years after the biosimilars pathway became law. That is a long time, even for Senators.

Dr. Marks and Dr. Woodcock, why is this taking so long? Either one.

Dr. MARKS. Well, I can start and I can let Dr. Woodcock continue.

In part, it was necessary to develop—the guidance took time to develop in order to develop the science behind this. There were issues with developing the science of determining that things were bioequivalent. There were issues in determining what constitutes the scientific criteria that things would be interchangeable.

Taking into account stakeholders' comments on these, and so, it did take some time to get things, but I think we are committed to moving ahead very expeditiously toward trying to get out our required guidance and to continue to move ahead with this important program.

Senator ROBERTS. Not an easy task, I know.

Please, doctor.

Dr. WOODCOCK. We would expect to finalize the guidance ahead of schedule. That is what I would expect.

Senator ROBERTS. Thank goodness.

Dr. WOODCOCK. I would expect that there is going to be, there is a great deal of controversy on this, obviously, because it is a point of great financial import to both innovators and the biosimilars.

The patients are very interested in this. All professional groups are interested in this. So there is a great deal of commentary on what the standards should be.

We are committed to getting this done as quickly as possible and it should not, it will not impede the availability of biosimilars on the market. It is simply switching at the pharmacy that is the interchangeability piece.

Senator ROBERTS. In 2015, only 9 percent of generic drug applications were approved in the first cycle review.

Dr. Woodcock, before the Energy and Commerce committee, you stated that you think that this number is either 20 or 25 percent of the new agreement. You would consider that a success.

In the commitment letter, I see the pre-application program for complex products as a good step to improve early communication for companies with the agency and approve on review success. But that is only for complex products.

Can you share any other efforts within this agreement that would be beneficial for noncomplex products to receive the first cycle review approvals?

Dr. WOODCOCK. Certainly, we recognize that even more communication than we have instantiated in the first generic drug review program will be necessary to bring up that first cycle approval rate. And it is in our best interests, as well as the interests of the companies and the public, to get these on the market as quickly as possible.

We have put in place more communications at every step of the way, including if people do not get a first approval, there can be a conversation about what was wrong, what needs to be fixed, and so on. We hope this will improve first cycle performance faster than we did in PDUFA.

Senator ROBERTS. Mr. Chairman, I would like to acknowledge your aversion to acronyms. And I would like to acknowledge your penchant for country and western music. I would like to acknowledge the considerable fervor that has been shown on the minority side. I do not know if this is the best I can do. I will work with you later.

“We met in PDUFA,
But she was very aloofa.
But our bios were similar,
So we got married in GDUFA.”

[Laughter.]

What do you think?

The CHAIRMAN. I think we should go onto Senator Warren.

[Laughter.]

As much as I respect your country music.

Senator ROBERTS. I think that is probably a very good idea.

The CHAIRMAN. Thank you, Senator Roberts.

Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman.

You have called us here today to discuss the FDA User Fees program, and it is vitally important, and I am going to work hard to make sure that this makes it through Congress.

I join my democratic colleagues and—I am just going to be blunt about this—I have no idea why we are having this healthcare hearing today, 48 hours before the House Republicans try to ram through a bill that is going to rip health insurance away from 24 million people, raise insurance premiums for seniors by \$12,000 a year, and eviscerate the Medicaid program to the tune of \$880 billion. There is no indication that the Senate will hold a hearing on this bill. Not now, not ever.

If Republicans want to gut our healthcare system, they should have the decency to talk openly about it, not jam through a bill that will devastate the entire country's healthcare system with zero debate.

We have three distinguished witnesses here from the Food and Drug Administration. None of this is their fault. I do have some questions I want to ask them, so I am going to do that. But they are among the thousands who work hard at the FDA to get innovative treatments to patients, while also protecting us from dangerous drugs, from deadly devices, and from poisoned foods.

Dr. Woodcock, on his third day in office, President Trump announced a governmentwide freeze on hiring. Does a hiring freeze help or hurt the FDA's ability to do these jobs?

Dr. WOODCOCK. We are actively working through the issues of hiring with the Administration. We were able to move forward on certain select positions within the User Fee programs and to hire to meet also the needs of the Cures Act.

Senator WARREN. That was not the question I asked.

The question I am asking you is: does a hiring freeze make it easier or harder for you to do the things you are supposed to do? Protect us from dangerous drugs, from deadly devices, and from poisoned food.

Dr. WOODCOCK. Clearly, the FDA needs adequate staff in order to conduct its public health mission.

Senator WARREN. All right. That is the whole point of these User Fees is that it is supposed to add positions to do drug and device review, not plug holes that are created by a hiring freeze.

Let us be honest. We have to say there is no way that a hiring freeze is going to help the FDA do its job.

The President's budget also proposed to, quote, and I will read it here, "Replace the need for new budget authority at the FDA with an increase in medical product user fees." As I read this, I think this is just a fancy way of saying that Congress should cut the guaranteed funding going to the FDA.

Dr. Woodcock, if Congress cuts funding going to the FDA, does that make it harder or easier for the FDA to do its job?

Dr. WOODCOCK. I am not position to discuss budgetary matters at this time.

Senator WARREN. Well, I get that you are not here to describe the budget, but I am asking you a question. If the President wants to cut money going from Congress to the FDA, is that a good idea or a bad idea from the point of view of the FDA doing its job?

Dr. WOODCOCK. Again, I am not able to comment.

Senator WARREN. Well, look. I really do not get what the plan is here. I certainly hope that we are not going to blow up our User Fee negotiations and risk an FDA shutdown because the President

does not think that the Government needs the Food and Drug Administration.

I am not seeing much evidence that this Administration actually wants the FDA to work. If they did, they could start by reversing the hiring freeze and backing off this announced reckless plan to undermine FDA funding.

Let us be clear, if the Republican bill to gut American healthcare becomes law, all the miracle cures and speedy FDA approvals in the world will not matter to the tens of millions of Americans who will not be able to afford them when they get sick.

On behalf of the thousands of people in Massachusetts and millions of people around this country who are terrified about that, Mr. Chairman, I look forward to having a Senate hearing where we can discuss those issues.

Thank you.

The CHAIRMAN. Thank you, Senator Warren.

I will take my 5 minutes now, if that is all right with Senator Cassidy and Senator Scott.

Senator SCOTT. We serve at your pleasure, Sir.

The CHAIRMAN. No, you do not really.

Senator SCOTT. I concede your right.

The CHAIRMAN. I appreciate your courtesy.

We scheduled this hearing on March 3 because of what would happen if we do not do our job here. I am going to ask you a question in just a moment of what the consequences would be to patients all over the country if by July 27 we do not decide what we think about these Agreements and you have to fire 5,000 people. What the consequences will be to the enormous advances that we laid in place for the 21st Century Act. I will ask you that in just a minute.

As far as the FDA hiring freeze, I can answer that question. That is a problem. That needs to be lifted as soon as it can be because one of the major advances of the 21st Century Cures Act was to give the FDA new authority to hire the people it needed and pay them what needed to be paid to them so they could approve the drugs that we complain are not getting through the investment and regulatory process and into doctors' offices.

I can give my opinion on that and that is my goal. I hope the Administration will quickly recognize the importance of that.

Insofar as the amendments to the Affordable Care Act, without dwelling on that, because I want to spend the time here on this important Act, I think we can do two things at once in the U.S. Senate.

It is true there. We proceeded on two tracks when we passed the Affordable Care Act. One was the part that required 60 votes. There were plenty of hearings there.

One was the reconciliation track. There were almost none there. In fact, there was no train that ran through the Congress faster than the Obamacare reconciliation bill. It went through in 8 days. Budget to the floor, budget to the floor in the Senate, and then back to the House, and out to the President.

There has already been much more deliberations on the current amendments than there were on that reconciliation in 2010.

On the part that requires 60 votes, which is the only way we will get lasting, durable changes to our healthcare system, there will have to be a lot of hearings. We had one a month ago in what I consider the real humanitarian crisis, which are the 231,000 Tennesseans who will have zero healthcare options in 2018 if Congress does not act to fix the problems of what is a collapsing, failing individual market caused by the Affordable Care Act.

We proceeded on two tracks in 2009 and 2010. We are proceeding on two tracks today. The track on reconciliation actually has more deliberations than the one did in 2010.

Let me ask my question. What would be the impact if Congress does not act by the end of July, 60 days before the expiration of the current Agreements? What would be the impact on the Food and Drug Administration if we fail to do that? I will ask each of you that question.

Dr. WOODCOCK. We would have to follow the Government rules for preparing to let go a large number of people, as you said, across the User Fee programs because we would have to prepare to issue notices of reduction in force if those User Fee programs were not reauthorized, and we would not be getting the money.

There are carryover balances that are carried within each of the programs that allow for an orderly shutdown.

But I think your question is more what would the impact be?

The CHAIRMAN. Yes. What would the effect be on patients, and on new drugs, and on lifesaving devices?

Dr. WOODCOCK. Peter, do you want to start?

Dr. MARKS. We have literally hundreds of investigational new drug applications that are a part of User Fee programs. The ability to hold meetings in a timely manner, the ability to make sure those approvals happen in a timely manner to get products to patients with medical need would be adversely impacted severely.

The CHAIRMAN. Dr. Shuren.

Dr. SHUREN. We would lose about one-third of our people. And it is not just that reviews will take longer, but the industry, which now is starting to bring their innovative technologies to the United States early, sometimes first, as you heard with the artificial pancreas. They are going elsewhere. I am already hearing from companies if the United States does not work out right, it is not just Europe, it is now China and elsewhere.

The CHAIRMAN. I am not exaggerating when I say that if we do not act, if the President does not sign the bill by July 27, I believe it is, then you have to take these steps.

Is that correct?

Dr. WOODCOCK. We must initiate them. Yes, we must do the reduction in force that would start at the time.

The CHAIRMAN. So you send letters to employees saying, "You are going to be laid off in 60 days."

Is that right?

Dr. WOODCOCK. We would begin a process to do that, and we have to identify the people. There is an elaborate system of how you figure out who is what. But everyone would know this is going on.

The CHAIRMAN. An application for a cancer therapy or cure that might be before reviewers might be delayed?

Dr. WOODCOCK. Yes. We know right now, we have patients living sort of hand to mouth, young people with brain tumors or other cancers who are waiting for the next effective therapy to come along as they develop resistance to current.

I heard from a Senate staffer, ex-staffer about this who has lived a long time, been able to work because there have been successive approvals of drugs for his cancer that have kept him alive. And this would be repeated over and over.

Most concerning in the biologics area for the pharmaceuticals, the gene therapies, the cellular therapies, the very innovative treatments require oversight in the investigational phase because any slip up there can last for 10 years and set the entire field back.

The CHAIRMAN. Thank you very much.

Senator Hassan.

STATEMENT OF SENATOR HASSAN

Senator HASSAN. Well, thank you, Mr. Chairman and Ranking Member Murray.

And thanks to the witnesses for being here today as well.

I will join my colleagues on the minority side of the table here just to reiterate that while I think it is extremely important that we consider the User Fee Agreements—and I appreciate the chance to speak with all of you today—like many of my colleagues, I am troubled that the committee has not been, and is not addressing, the issue that I hear most about from Granite Staters right now.

I just came back from several days at home and wherever I go, people want to understand what the implications of Trump Care are for them. I hear from constituents all the time who, because of the Affordable Care Act for the first time, got access to lifesaving treatment.

While what you all are doing and what we are talking about here today is very important, without that underpinning of insurance coverage for many of my constituents, this is a little bit of an irrelevant conversation.

I hope that we will have a chance to convene hearings to the Chairman's point that the U.S. Senate can do two things at once. We could convene some hearings on Trump Care before we have to vote on it, and I hope very much that we will do that. Not only so we can make informed decisions, but so that all Americans can be part of an open and transparent process because the Trump Care bill, as it now stands, will hurt my constituents. It will hurt our country.

As the committee in this body with jurisdiction over many things in the Trump Care bill, that is the topic that I think we should be focused on today.

With that being said, I do want to ask you all about a couple of things and I will start, Dr. Woodcock, with you.

Too many Granite Staters, and people across our country, are struggling with an opioid addiction and it is an epidemic in my State. It killed approximately 500 people in the little State of New Hampshire last year.

I commend the FDA for putting out its Opioid Action Plan last year, but I want to be very clear that there is still much more work

that the FDA needs to do on this issue, and that it continue to play a role in confronting and beating this epidemic.

For example, there are several FDA-approved opioids with so-called “abuse deterrent formulations” on the market. And the User Fees that we are talking about today help pay for review of these products.

The FDA acknowledges “abuse deterrent” does not mean “abuse proof,” and has acknowledged that these products can still be easily abused by just swallowing a whole bunch of the abuse deterrent drugs, for example.

Dr. Woodcock, is it appropriate to call these opioids abuse deterrent if they can still be easily abused?

Dr. WOODCOCK. They cannot be abused as easily in certain ways by snorting or by injecting, which are preferred by many addicts because they give you an immediate high.

Senator HASSAN. Right.

Dr. WOODCOCK. All right? What we are trying to do is move up the scale and get more and more effective abuse-deterrent technologies in place. These are Version 1.0. We acknowledge that. They are still undergoing their evaluation to see, in fact, how effective they are.

Senator HASSAN. Just so I can understand. They are just as addictive, though.

Dr. WOODCOCK. They are opioids, and so what we are trying to do in addition to introducing more treatments for opioid abuse is to introduce pain treatments that do not have these liabilities. And we have approved a number of drugs for specific conditions that now people are, like the neurologists, are moving away from opioids for peripheral neuropathy, for example.

Senator HASSAN. Right. And I understand that, and that was actually going to be—so thank you for anticipating one of my questions. I am very glad you are doing that because I have been talking with my constituents about this, both as Governor and now as Senator for some time, and I think that is very welcome news.

I do want to get back to one issue, though, which is the use of the term “abuse deterrent” because experts have done surveys now that show that 46 percent of primary care providers think that abuse deterrent products are less addictive than other opioids.

In light of this safeness conception, do you think calling these products “abuse deterrent” is misleading or causing providers to think that these products are less addictive?

Dr. WOODCOCK. It certainly seems as if more education is needed, and that is something that we are working on very hard. We are considering extending our educational program. Over 100,000 I think, practitioners of various kinds in healthcare have been educated under our current program. But we would like to extend that.

Much of the abuse, though, of opioids is not these high potency extended release, but is actually the kind of drug you get after you go for an in-and-out procedure, or you have your tooth extracted. And the question is, do you really need 60 tablets with three refills?

Senator HASSAN. Right.

Dr. WOODCOCK. The healthcare system is actually awash and actually people’s medicine cabinets are full of these products that are

not the high tech products. They are the simple opioids. They are just as addictive.

Senator HASSAN. Right. My time has passed, but I think to that point, I would look forward to working with all of you on the FDA taking a greater educational role.

Because one of the issues we have had with providers, especially with licensing boards, is pushing them to change their proscribing guidelines. So that somebody getting wisdom teeth extracted are leaving with only 1 or 2 days' worth of prescriptions rather than a month or two.

I would look forward to continuing to work with all of you on that.

Thank you.

The CHAIRMAN. Thank you, Senator Hassan.

Senator Cassidy.

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. Thank you all for the good work that you do. As a physician, I am very aware of the good work that you do, so thank you.

Dr. Woodcock, you mentioned that the GDUFA II includes preapproval meetings, but it seems, at least I am told, the process still lacks clear guidance on what tests a complex generic has to pass.

Also pre-NDA meetings are limited to applicants who have already started investment and can meet the several requirements. Rankly, this throttles out a small business, the guy in his garage and the gal coming together seem a little bit iced out by that, if you will. Only the bigger firm that already has the pockets can address this.

I guess how does this make the process more transparent or competitive? Thoughts?

Dr. WOODCOCK. Well, first of all, we are trying to commit to having within several years of the brand product being approved, having guidance out there that is basically a recipe for how to develop the generic. For the vast number of generics, that would be enough; that sort of cookbook.

For the complex ones, we do not know either, or completely, how to make a copy. We do have small business assistance, which is a separate program outside of what we are doing in the pre-generic area. That might be an appropriate venue for somebody who is just getting started and really does not know the ropes at all. So that opportunity is also available.

Senator CASSIDY. Because it does seem as if that is a little bit of a hold up like Mylan and Advair, et cetera, in terms of coming up with a generic. How would you pass FDA muster?

Is there a way to actually give guidance without being prescriptive because there is going to be somebody that may have a better idea? Do you see what I am saying with that?

Dr. WOODCOCK. No guidance, actually, is prescriptive; people are very confused about this.

Our draft guidance is not binding on us or on the applicant, and neither is our final guidance. And so if somebody comes up with a better way, we are happy to entertain that.

The guidance is simply for those who are not clear what we are thinking to make them clear about what we think would be an acceptable way. But there are other ways that are certainly acceptable. I agree with you. So they are not prescriptive.

Senator CASSIDY. OK. Also, we have spoken in the past about post-marketing surveillance. GAO just recently issued a report, or I should say last year, that the FDA,

“Lacks reliable, readily accessible data on track safety issues and post-market studies needed to meet certain post-market safety reporting responsibilities, and to conduct systemic oversight.”

Any response to that? Clearly and the reason I raise this, of course, personalized medicine will increasingly—if we are going to get it out the door, as we have spoken before—require maybe we get it out the door, but there is a tension as to the safety.

If the data systems are inadequate, how will we meet that tension?

Dr. WOODCOCK. Well, they were talking about our tracking system, so we can roll up all this and make reports. I think we are pretty satisfied that our actual oversight of safety since the Amendments Act has been really strengthened. It is very robust.

In October 1, 2017, I hope we will enact a workflow management system for new drugs. We still do not have that. We do not have an I.T. system for the new drug review process.

We will be implementing that and over time, we will put these track safety issues—tracking them, tracking other safety issues and so forth. All will be put into this I.T. system that we will be implementing, hopefully, in October 1 of this year. That will then address the GAO concern.

It was really about our I.T. systems and the fact that—which is true, I think, across much of Government—that they are not up to what you would find in the private sector.

Senator CASSIDY. Dr. Shuren, the FDA also has a similar system, the NEST system, we have spoken of.

Will it be part of this October 1 rollout or do you feel like you already can do adequate reporting?

Dr. SHUREN. This is a differing system separate from what came out on the drug report. But we do think that NEST is going to provide complementary tools to what we have today.

Today most of our reporting is passive. It requires a person that is going to have to identify if there is a problem and then take the time to report it in.

NEST is going to allow us to move more toward an active surveillance system where we can go through larger datasets with analytical tools to try to find if there are associations between the use of a device and particular safety problems.

Senator CASSIDY. OK. Thank you. Yield back.

The CHAIRMAN. Thanks, Senator Cassidy.
Senator Whitehouse.

STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Thank you, Chairman.

I guess, Mr. Chairman, we are going to find out this week whether the so-called Trump Care bill can get through the House of Representatives and come over to the Senate.

If it does, I would like to recommend that we follow the model that you led, that I thought was extremely successful on the Elementary and Secondary Education bill where we had hearings, and we worked together under your and Ranking Member Murray's leadership. We put together a really significant piece of legislation that has now passed into law.

Sometimes when we get together, the stuff we can agree on, we can agree on because it is so much of a "nothing burger". This, actually, was a very consequential piece of legislation that we were able to agree on, and I can even remember your reaction the day that we voted it out of committee unanimously. I think we have a good model in this committee for treating major legislation in a responsible way.

I would note that when we did the Affordable Care Act, this committee was also very, very active. I was appointed to it on a temporary basis at that point so that we could fill out a seat where we had a vacancy. I participated in weeks of hearings in this very committee on the Affordable Care Act. My recollection is that we considered, and even adopted, more than 100 amendments, many of them bipartisan. In fact, I suspect almost all of them were bipartisan in order to be adopted.

This committee was active, and had an active and vibrant role in considering the Affordable Care Act.

This thing is coming out of the House at us. It looks like it is a complete mess. It has never had a proper hearing other than a kind of "Midnight Spectacular" that the House, I guess, developed just for this particular bill to jam it through.

At least speaking for Rhode Island, we are now calculating if that mess were to pass into law, we would lose \$30 million in Medicaid. We would put people, 70,000 Rhode Islanders who are on the Medicaid expansion, at risk. We have 30,000 Rhode Islanders who are in the individual market as a result of the Affordable Care Act. Ninety percent of them are enjoying tax credits that come from it. It is supporting their ability to afford healthcare.

One of our insurers, Neighborhood Health Plan, has dropped its premiums. It is the low income serving insurer in Rhode Island. In fact, they tried to drop their premiums even more and our Insurance Regulator said, "No, no, no. You can drop them a little, but let us not go too far now." There may even be more premium reductions coming.

Our exchange is working. The idea that this wreck of a piece of legislation is going to be fired like a torpedo at my State without my committee even having a chance to consider it is pretty objectionable when you consider how well we did with the SSA and how active this committee was with respect to the Affordable Care Act.

I hope, frankly, I hope this thing dies over in the House and gets the proper end that it deserves. But if it does come over here, I would really encourage the Chairman and the Ranking Member to find a way to have meaningful hearings on it.

To the witnesses, my recollection from our previous conversations was that when I spoke to the Drug and the Device sides individ-

ually, both of you said that we would be better off with a third track. Neither side was willing to propose a third track, but you did urge that we try to come up with a third track. At least, that was my recollection of the State of play.

We could not get that organized. In the 21st Century Cures Act, instead, we asked for improved coordination between the two tracks.

Can you tell me (A), how is improved coordination working? And (B), if we could, would you still like us to develop a third track? Is improved coordination Plan B, and should we still be considering a proper, thought through, well-developed third track for drug-device combinations?

Dr. WOODCOCK. Go ahead.

Dr. SHUREN. I do think coordination across the agency has improved. The agency has created a Combination Product Policy Council. It has now been changing processes, putting policies in place to have much more coordinated activities.

For example, the agency has already modified how we consult various centers, and we have timeframes that we have piloted, and where we will have that fully stood up as a program fairly soon. The early data on it is showing that it is helping.

In terms of your question about should we explore still another pathway? Right now, our biggest focus is on implementing 21st Century Cures and seeing what comes out of that. We are always open to other ideas to make the programs work better, and always happy to discuss other ideas.

The CHAIRMAN. Thank you, Senator. You took most of your time on another subject, but that will be fine, if that is what you want to do.

Dr. WOODCOCK. I agree with Dr. Shuren. Yes, I agree with that.

The CHAIRMAN. Go ahead.

Senator WHITEHOUSE. No, it will take too long. That is all I needed to hear.

The CHAIRMAN. Give him an answer. He deserves it. Is that a sufficient answer?

Senator WHITEHOUSE. Sufficient to me, as long as there is not pressure for us to develop a third way right now, that they would rather work through this first. I think that is our understanding.

The CHAIRMAN. Actually, if I might just add, that is of interest to a great many of us on this committee. Being able to let you work through the best ways to do it, before we jump to a different pathway might be the more practical approach. I appreciate the Senator's questions.

Senator Scott.

STATEMENT OF SENATOR SCOTT

Senator SCOTT. Thank you, Mr. Chairman.

Thank you all on the panel for your dedication and your commitment to the welfare and the health of America and American citizens. Appreciate that.

Dr. Woodcock, the PDUFA VI goals letter encourages the adoption of a new drug discovery tools under the mid-provision. This is important as I feel all too often the private sector and researchers are innovating, but the Federal Government is often behind on rec-

ognizing the value and impact of these tools. In short, we are missing some opportunities.

A good example of an innovative tool in this space is tissue bioprinting, which began at Clemson University in South Carolina, of course, my home State. It is now being used by the pharmaceutical industry, researchers, and the NIH.

The goals letter does not distinguish between ready to go technologies, those that hold immediate promise and are already being used, versus those technologies that are not yet quite available.

How will the FDA differentiate and prioritize its selection of technologies that help make drug development shorter and less costly? And will you make efforts to understand tools that are being used already when deciding which tools you should consider?

Dr. WOODCOCK. Certainly. What we are contemplating is that people will approach us with the tools that they would like to get qualified for regulatory use.

Typically, though, academia has one sort of standard for tools. We do not just publish papers on the tools. We have to make decisions about human life. And that is a little bit higher standard of rigor often.

If we are going to depend on a tool to make decisions about what is going to happen, say, to somebody's kidney or maybe their brain, its performance has to be pretty well-understood. That is what our qualification process is about.

To answer your question, we expect people will approach us with qualification proposals. That is happening now. We have a program going on, and so we will give them advice. That is what was contemplated in this program. We will give them advice about what they need to do to get up to the standard that would be needed to make decisions about human life based on that tool.

Senator SCOTT. I think your answer, in many ways, reinforces the necessity of using those tools that are already in the market or ready to go to market as opposed to those that are still in the development stage, actually.

These 3-D tissue models also promise to have a big impact on drug safety and cost, which is what you were just discussing.

Given that it often takes more than a decade and billions to research and develop a new drug, we should make sure that we are encouraging the use of any tools available that can help sponsors identify potential toxicity issues early in the clinical trials process. This not only improves drug safety, but saves money as billions are lost every year in the last stage clinical trial failures.

How do you plan to give product developers confidence that you will accept the data being generated from these new tools?

Dr. WOODCOCK. That is what the qualification process is about. In fact, right now, the C-Path Institute has a big safety consortium, and they have tools before us just as you said. Better safety tools to look at drugs earlier and determine whether there is a safety signal. Some of those have been qualified already for animal use and they are in the human process right now.

Safety tools are about the most important, as you said. We are also working with NIH and others to develop that evidence standards to say, "How much do you need to know to rely on this, to

keep somebody's kidneys safe or their heart safe, that you make decisions on that?"

That along with the process that we have set in place will enable people to have a clear path of how they develop these tools into something that can be used for regulatory purposes.

Senator SCOTT. Thank you. Final question, Mr. Chairman.

The pioneering work of Clemson researchers in the field of tissue bioprinting and the promise of that technology in the drug development and review process is a great example of the benefits of promoting a strong classroom to lab, STEM education pipeline.

I am aware of the FDA's practice of collaborating with academic institutions to create a CERSI in order to enhance the regulatory workforce and promote innovation and regulatory science.

Just this year, I believe, the FDA invested about \$6.7 million in the creation of a CERSI with Yale and the Mayo Clinic.

My question is, can you comment on the value of the CERSI program in evaluating the safety and effectiveness of the products the FDA regulates? And given the level of investment in these Centers, how does the FDA plan to ensure accountability from this program?

Dr. MARKS. The CERSI programs have been a wonderful way for our scientists to interact with other investigators. I think they have helped to develop the evidence needed to look at safety in various ways. I think they continue to blossom.

Just so you know, the CERSI's are not the only ways that our investigators are involved with academic institutions. We have many collaborations that are done as part of cooperative research and development agreements across all of the Centers that help us to have a critical interaction that keeps us at the forefront of the science that we need to know in order to speed the development of products.

Senator SCOTT. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Scott.

Senator Kaine.

STATEMENT OF SENATOR KAINE

Senator KAINE. Thank you, Mr. Chair and thanks to the witnesses.

Mr. Chair, I echo the comments made by folks on our side about the timeliness. This hearing is very important. This topic is very important. But I would say there is kind of an elephant in the committee room, which is, there is a matter of both importance, but desperate urgency before Congress, which is the House's consideration this week of the bill to repeal Obamacare and propose a particular version of a replacement.

We are hearing that we may be asked to vote on that promptly here without, possibly without committee consideration on the floor.

When the Affordable Care Act was pending before this body, I was not in the Senate, but I understand the HELP committee held 13 hearings to really dig-in to the good, the bad, and the ugly of what we should do.

Mr. Chair, you did a good job. I was really impressed with the hearing that you called on the individual market, which is a chal-

lenging area that we ought to be working together to solve. That hearing was held before there was a plan on the table, so we were not able to talk about whether this plan addressed it.

There were four witnesses who were here that day at that hearing and I asked them all the same question. They had all had thoughts about how to fix the individual market. And I said, "Would it be a disaster for the individual market if we repealed the Affordable Care Act?" They all said, "yes". And then I said, "But we do need to fix it." They all said, "yes".

And I said, "OK. If we are going to fix it, should we fix it fast, careless, and secret? Or, should we fix it slowly, deliberately, and transparently?" They laughed at my question because it was so obvious the answer was, of course, slow, deliberate and transparent.

The notion of taking an action on a bill that might cause 24 million people to lose health insurance, and that is the combined population, the combined population of about 16 States does not do credit to a body that is often called the world's greatest deliberative body.

I once heard Senator Franken say, though, sometimes the world's greatest deliberative body spends more time deliberating on whether it should be Senate bean soup or tomato soup in the Senate dining room than on matters of great importance.

Senator FRANKEN. My version was much funnier.

[Laughter.]

Senator KAINE. Yes, well, as evidenced that I did not get a laugh.

Anyway, this is something that if there is to be a world's greatest deliberative body, could there be anything more important to deliberate on than people's health?

On the issue before us, the President's budget submission last week proposed a cut of the NIH budget to the tune of \$6 billion. Often drugs that are developed through the FDA process have been significantly assisted or sort of started with the assistance of NIH funding.

Am I correct about that?

Dr. WOODCOCK. Generally what happens is NIH researchers who get grants lay the foundation, the scientific foundation, understanding the pathways, or the pathophysiology. And then drugs are separately developed against that.

Senator KAINE. The title of this hearing deals with innovation, improving medical product regulation and innovation.

Would a budget cut of that size to the NIH hurt the innovation that is one of the subjects of this hearing?

Dr. MARKS. Unfortunately, we cannot speak to the budgetary implications of that.

Senator KAINE. Well, boy, that is going to have me do a followup question because you guys are here for expertise.

Do you have no opinion about whether there is a connection between NIH funding and medical innovation?

Dr. MARKS. I can say that clearly there is a connection between NIH funding and medical innovation, and that innovations from the NIH have supported the development of important products that have benefited the lives of people in the country.

Senator KAINE. So, as a general matter, reductions in NIH funding would have the effect of reducing innovation as a general matter?

Dr. MARKS. I would have to leave you to surmise that.

Senator KAINE. Do you not have an opinion on that question?

Dr. MARKS. I am sorry. I cannot speak to it.

Senator KAINE. Do you any of you have opinions on that question, whether the reduction of funding to the NIH as a general matter will reduce innovation?

[No response.]

Do I assume that none of you have opinions on that question as professionals?

Dr. WOODCOCK. We are just not in a position to discuss it.

Senator KAINE. Let me ask a second question, a second topic. Drug pricing is a serious concern for everybody here and drug pricing of biologics is one of the matters that we are very concerned about. They are innovative, but they can be expensive too.

Of the 595 drugs paid for by Medicare Part B in 2015, only eight biologics accounted for 40 percent of the total Part B spending.

Talk to us about moving forward within the FDA on biosimilars, regulatory guidance for biosimilars so that we can potentially see, through the development of those products, a reduction in drug pricing.

Dr. WOODCOCK. The Biosimilar User Fee program that is part of the subject of today's discussion, of today's hearing, supports our approval of new biosimilars in setting the standards for those coming on the market.

They, of course, are more complex molecules than what is approved under the generics program. And they have required an entire set of scientific principles be developed, which we have done. That has stimulated, really, a new industry to come forth and develop products.

We have approved four biosimilars. We have about 13 applications before us, and there are 64 development programs where people are working to show their biosimilar work to various innovator drugs.

This is a rising industry. We recognize that it will take a number of competitors to each brand product to substantially bring the price down, if that is similar to the generic market.

Senator KAINE. Thank you. Mr. Chair, if I could just—

The CHAIRMAN. We have a vote at noon and we have one more Senator who has to speak.

Senator KAINE. I am just troubled by the witnesses' unwillingness to offer professional opinions. They are M.D.'s and Ph.D.'s and I am new to the committee, but I am on the SASC committee and our military witnesses all the time give us their professional opinion, even when it differs from the Administration. We never ask them about what they communicate to the Administration. That would not be fair.

We do call professional witnesses before a committee with a thought that they will give us their best expertise. I find it impossible to believe that the individuals do not have an opinion on the question of whether the funding of research has a connection to

medical innovation. And whether the cutting of research funding would, as a general matter, reduce innovation.

The CHAIRMAN. Yes, in defense of the witnesses—both this Administration and in the last one—the military officers have a different role and give different answers.

The nonmilitary officers always are in a tough spot when presented with questions like that because they have been instructed by the Office of Management and Budget not to answer the question. Maybe it should be different, but that has been the tradition throughout both of the last, well, all the administrations I know. Senator Franken.

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. The answer is yes, reduction in NIH funding would have a reduction in innovation. And I am an expert. I am not.

By the way, the joke is that sometimes the Senate is not even the most deliberative body in the Senate. Sometimes it is the Senate dining room when it has to decide whether turnips will be part of the winter vegetable medley. That was the original joke, and it is not real funny, but I wanted to deconstruct what a joke is, but we can do that at some other time and this is why we need more research at the National Institute of Comedy.

The hearing today is on the User Fee Agreements that industry and the FDA forged to support the agency's operations and approve performance accountability. This is really important. That is very important and we should work on a bipartisan basis, as this committee often does. I thank both the Chair and the Ranking Member for that.

Frankly, I came in—I walked in. I had been at the Supreme Court, the Gorsuch hearings. So I am sorry I got in here so late.

I think what the Senator from Virginia was talking about was that we really should be talking about ACA and about healthcare reform. I am surprised that we are not doing that. I thought that we had a very good hearing.

I agree with the Senator that we had a good hearing on that and I thought the Chairman was absolutely right. That what we should be looking at is the exchanges. I think that is what we should be doing over here right now because we are in the middle of this really seismic debate and battle. What I see in the House that is being passed again, or being taken up in a way that is not the way, I believe, the health bill should be is what we should be talking about.

This past weekend, I was in Minnesota and I did roundtables in Perham, MN at their hospital. Did a roundtable in Moorhead, MN at the nursing home and my goodness, people are very scared by what they are seeing and these are uniform. People were crying at this. And so, so concerned and this is what we really should be talking about, I think, right now, as important as this issue is.

I want to thank Dr. Woodcock, who has testified for us and Dr. Shuren especially. I want to tell you what a big difference you have had in your role, in terms of the medical device industry, they tell me uniformly that you have been a wonderful partner.

Before, when I got here in 2009, the cultures were so different and that you have worked so hard to help bridge that. So thank you for that.

I really do, I just hope you are hearing me, Mr. Chairman, that I think that we should be looking at those exchanges and how to fix those. I think that is the first thing that we really need to be doing. I am afraid that there is a bit of trying to cause destruction by the way this is being taken up now in the House and by the President.

I want to talk a little bit about, since we are here, postmarket surveillance. I spent a minute on the theory of humor, so I am sorry. I will try and make this quick.

One of the reasons the FDA launched NEST was to enhance FDA's post-market surveillance activity. One early report issued by the FDA explained that the purpose of NEST was to enable,

“Active surveillance in near real-time using routinely collected electronic health information, quickly identify poorly performing devices, and facilitate the development of new devices and new uses of existing devices.”

While I am encouraged that the most recent MDUFA agreement funds NEST, the funding is restricted to activities that just promote premarket approval.

My understanding is that this User Fee funding would complement work FDA has underway already to advance NEST's post-market surveillance capabilities.

Is that true and can you provide me specific examples of what you are doing currently to promote more active postmarket surveillance through NEST?

Dr. SHUREN. The answer is yes. And just to clarify, the commitment letter for MDUFA talks about use of real-world evidence in NEST. And because it is under MDUFA, the activities that we would commit to, or the NEST coordinating center commits to, has to be within the scope of MDUFA, which is predominantly premarket review.

However, the NEST coordinating center beyond that is also focused at activities that go more toward traditional postmarket surveillance.

What we have been doing already is trying to leverage real world data sources, for starters, for conducting some of our required postmarket studies.

One of the challenges we face today is once we approve a device, patients do not want to sign up in clinical trials. But if we are already collecting that data as a part of routine clinical care, and we can make good use of it to understand the true benefit and risk profile of the device, that is a win for everybody. We can do it at lower cost, and we can finally get the answers we have been trying to get for years, and we are starting to do that.

Senator FRANKEN. Because I just cannot emphasize enough how important, I think, postmarket surveillance is in terms of people's safety and the efficacy of these devices.

Thank you, Mr. Chairman, for your indulgence.

The CHAIRMAN. Thank you, Senator Franken.

There are 10 minutes left before the close of the vote.

Senator Murray, do you have closing comments?

Senator MURRAY. I would just say this, and I will submit my questions to the record.

Again, I just have to emphasize how concerned I am that a major piece of legislation is being jammed through in the House. It is going to come to the Senate, reportedly next week with changes, again, before the Senate considers it or sees it, rushed through in a few days and a few amendments. And we have had no hearings in the Health Committee.

I, like all of my colleagues, am hearing from so many people who are deeply concerned and frightened. This is a bill that, I understand, impacts 20 percent of our economy, healthcare. We should be having a hearing about the impacts of that, whether it is Medicaid, taking away the Medicaid expansion, or changes to that program. How is this going to work?

I heard from Linda on Bainbridge Island. She spent 15 years without direct healthcare coverage. Now has it. It is affordable, and she has had cancer; so a preexisting condition, critical to her.

Monica from Seattle, increased cancer risk, could not afford preventive care. She needs that. Without coverage, she said she would just not be here.

Kim from Tacoma, her daughter and husband both have preexisting conditions, as do many Americans. They want to know what this bill will do to them.

I am deeply concerned that this Health Committee has not had a hearing and does not propose to have a hearing on legislation that impacts virtually every American.

The CHAIRMAN. Thank you, Senator Murray.

Senator WARREN. Mr. Chairman.

The CHAIRMAN. Senator.

Senator WARREN. Mr. Chairman, I also have another, I just have another question about a bipartisan bill that is being introduced today while we have FDA witnesses in front of us.

The CHAIRMAN. Sure. Please, go ahead.

Senator WARREN. Would you like me to do it now?

The CHAIRMAN. Why do you not do it now?

Senator WARREN. I will try to do it, and I will try to do it without being funny, so we do not have to laugh. OK. Thank you.

Forty-eight million Americans, 48 million, have some level of hearing loss and this includes half of all people in their 70s. If hearing loss seems like a boring problem, I want you to think about what it means to be unable to participate in a meaningful conversation with another person, unable to talk on the telephone, or to hear a television or a radio.

People with hearing loss are more likely to experience social isolation. They are more likely to experience depression. They are more likely to experience dementia. They are even more likely to fall, which is the leading cause of death for people over the age of 65.

The good news is that many cases of hearing loss can be corrected. Technology is advancing at an incredible speed. Hearing aids are smaller. They are more effective than ever.

Dr. Shuren, do you know how many of those 48 million people with hearing loss actually use hearing aids?

Dr. SHUREN. It is about 20 percent.

Senator WARREN. About 20 percent. Johns Hopkins researchers think it is actually about 14 percent, even smaller, but somewhere in that range.

The vast majority of people with hearing loss are literally suffering in silence. And there are a lot of reasons for this.

Do you know, Dr. Shuren, what it costs to get a hearing aid?

Dr. SHUREN. About \$2,000.

Senator WARREN. For each aid, that is exactly right. Out-of-pocket costs, it is not covered by Medicare, and most people need two of those. So that is \$4,000 to kind of get you in the door on this.

Earlier this month, Senator Grassley and I wrote an op ed in the "Journal of the American Medical Association" about this problem. And this morning, Senator Grassley and I introduced bipartisan legislation with Senators Hassan and Isakson that would help reduce the cost by directing the FDA to create a category of over the counter hearing aids.

Dr. Shuren, last December, the FDA announced, and I am going to quote it,

"A commitment to consider creating a category of over the counter hearing aids that could deliver new, innovative, and lower cost products to millions of customers."

Can you walk us through quickly why over the counter hearing aids could improve both access and affordability to hearing technology for Americans with hearing loss?

Dr. SHUREN. If we make it over the counter now, patients would not have to go through a healthcare practitioner. They could get it, let us say, from a pharmacy. Of course, as we reduce the costs of technology to come to market, and we have greater competition, we will see prices go down.

Senator WARREN. That is good to hear. Better access, lower prices.

It is good that the FDA is thinking about this. I am really glad to hear this. The legislation that Senator Grassley, Senator Isakson, Senator Hassan, and I have put together would help make sure that it actually happens. That these devices, when they are made available directly to consumers, that it is done in a safe and effective manner.

This is my last question. Can you just say something about the kinds of concerns you would want to be sure are addressed in order to make sure that this is done in a safe manner for people with hearing loss?

Dr. SHUREN. Well, we would want to make sure that patients understand how to use hearing aids, that we have good labeling to explain the circumstances under which they should contact their healthcare professional. We might also look at performance characteristics; should there be any output limits?

Senator WARREN. Right. I appreciate that.

We really do need to do this right. I know there are plenty of cases where over the counter hearing aids will not be appropriate. That is fine. But right now, there are millions of Americans whose lives could be made so much better if they had access to low-cost hearing aids.

This is a place where we could loosen up outdated regulation and with a few consumer protections put in place, we could actually let

the market work to help bring better products to people at lower costs.

Thank you very much.

The CHAIRMAN. Thank you, Senator Warren. Thank you for the legislation.

I want to thank the witnesses for coming and thank you for the work you do.

I think you can see from the attention on both sides of the aisle, how much we appreciate your willingness to move ahead with implementing the 21st Century Cures Act. Almost everybody on this committee, really almost everybody in the Senate, played some part in that because we saw the dramatic prospect of what would happen with the artificial pancreas for persons with diabetes, or a cure for HIV AIDS, or a way to identify Alzheimer's before symptoms showed; all of these Dr. Collins predicted before our committee, our Appropriations Committee, would likely see in the next decade.

Our goal is to try to move those lifesaving cures and devices more rapidly into patients' hands and into doctors' offices. We want to do what we can to create an environment where you are able to do that.

We mentioned the hiring freeze. I understand from staff that the Administration is already working with FDA to try to relieve the effect of that. I would encourage that and I will continue to encourage the Administration to be selective about a hiring freeze.

I understand about hiring freezes. When I was Governor, I put one on when I first came in. But the FDA, Dr. Califf told us that the single most important priority for him and the 21st Century Cures bill was the ability to hire experts to do the reviewing and to be able to pay them what it took to keep them so they did not go work for the drug companies, or some university, or somewhere else. So we want to make sure that we do that.

I wanted to ask, quickly, Dr. Marks. You mentioned regenerative medicine and I noticed how quickly you moved on that.

Do you think that the fact that your accelerated pathway is now available for regenerative medicine therapies or cures will bring a number of these therapies and cures into the FDA for more rapid approval and give people more confidence in the safety of those therapies and cures?

Dr. Marks.

Dr. MARKS. Thank you.

We are already receiving requests for the Regenerative Medicine Advanced Therapy designation. And we very much look forward to working with sponsors.

Normally, we cannot talk about unapproved applications. I can tell you that there is a sponsor who issued a press release yesterday that FDA had granted a Regenerative Medicine Advanced Therapy designation.

I think we have tried to move quickly on this and we look forward to continuing to move forward. We are thankful for the legislation that was passed that has provided this pathway.

The CHAIRMAN. Dr. Shuren, Senator Whitehouse mentioned the combination device-drug. I think we actually came to a pretty good way to move forward with that, which is to give you the opportunity to use your good judgment to talk across lines and see what

you can do within your existing authority. And then if we need to do more, which we may very well need to do, you could let us know that.

On guidance, Dr. Woodcock, I would make this observation. I think you said correctly that guidance, not only does not bind you, it does not bind anyone else. It is just guidance. But different parts of the Government have not been as clear as you have been.

I had a witness before me from the Department of Education on title IX who said that she expected all of the universities to follow her guidances as if it were the law. Well, of course, that was not even the Obama administration's policy, and when I talked to the Office of Management and Budget about that, they said, "We are doing our best to make it clear that guidance is not a regulation, it is not a law."

Maybe the FDA could explain that more clearly. That guidances are to be helpful, to answer questions, and if you have, the way you said it here, if you have a better idea, we welcome the better idea. Because I think a great many people are risk averse. They do not want to do anything that might delay things a year or two.

Is there something else that you might be able to do to make it clear what guidance is and what it is not?

Dr. WOODCOCK. Possibly. In the very front of every guidance document, it has a disclaimer and it says it is binding on neither party.

Maybe we could go further and really say in English, because this was bureaucratese, "If you have a better idea, come talk to us."

The CHAIRMAN. Yes, it might be that simple, just to put a headline on it. Say, "If you have a better idea, but in the meantime, here are some suggestions." Because that is what guidance really is supposed to be.

I appreciate my colleagues' concern about the Affordable Care Act and the amendments that are going through it.

The decision to hold this hearing was a bipartisan decision, and I am glad we held it. We are going to have another one in early April despite the fact that we have to confirm a Labor Secretary, and we have to consider the Affordable Care Act, and have a lot of other things to do, because it is hard to think of anything much more important than moving lifesaving drugs through the FDA and into medicine cabinets, and doctors' offices, and patients to save their lives.

That was the decision of this Congress, and President Obama, and Vice President Biden, and Speaker Ryan, and Senator McConnell last year, and it is still our opinions today.

I would make only this observation about the process of amending the Affordable Care Act, which I made earlier. There are two tracks to that and there were in 2009 and 2010. I was here.

The track that took 60 votes had lots of hearings, lots of discussion, lots of amendments. And the track that takes 60 votes now will have hearings, amendments, and we will see what comes out because only bipartisan solutions are durable.

The track in 2010 that went through the reconciliation process went like a freight train through Congress. I have never seen anything move more rapidly. It took 8 days, Budget to House, Budget

to Senate, back to the House, and onto the President. And that includes the weekend.

It is a little bit of selective memory here in terms of what is too fast when you are going through a reconciliation process. Actually, I believe the House of Representatives has done a very good job of discussing their legislation in public and before the Energy and Commerce Committee, before the Ways and Means Committee, before the Budget Committee, the Rules Committee, and it will be on the House floor.

Then when it comes, if it is passed in the House, we will see what happens in the Senate. If it goes to the floor, under the reconciliation process, there will be ample opportunity for amendment on the floor.

I thank the witnesses for coming.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time.

The HELP Committee will meet again tomorrow, March 22 at 9 a.m. to hear from Alex Acosta, nominee for Secretary of Labor.

Thank you for being here today.

The committee will stand adjourned.

[Whereupon, at 12:22 p.m., the hearing was adjourned.]