

EXAMINING FDA'S PRESCRIPTION DRUG USER FEE PROGRAM

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

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EXAMINING FDA'S PRESCRIPTION DRUG USER FEE PROGRAM

WEDNESDAY, MARCH 22, 2017

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

The subcommittee met, pursuant to call, at 10:15 a.m., in room 2322 Rayburn House Office Building, Hon. Michael Burgess (chairman of the subcommittee) presiding.

Present: Representatives Burgess, Guthrie, Upton, Blackburn, Griffith, Bilirakis, Long, Bucshon, Brooks, Hudson, Carter, Green, Engel, Butterfield, Matsui, Sarbanes, Schrader, Kennedy, Cárdenas, and Eshoo.

Staff present: Adam Fromm, Director of Outreach and Coalitions; Jay Gulshen, Legislative Clerk, Health; Carly McWilliams, Professional Staff Member, Health; Alex Miller, Video Production Aide and Press Assistant; Jennifer Sherman, Press Secretary; Danielle Steele, Policy Coordinator, Health; and John Stone, Senior Counsel, Health; Jeff Carroll, Minority Staff Director; Samantha Satchell, Minority Policy Analyst; Kimberlee Trzeciak, Minority Health Policy Advisor; and C. J. Young, Minority Press Secretary.

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

Mr. BURGESS. I ask everyone to take their seats. The subcommittee will come to order, and I will recognize myself for an opening statement for 5 minutes.

Today's hearing marks the Health Subcommittee's second opportunity to consider the reauthorization of several key FDA user fee programs. The Prescription Drug User Fee Act authorized the Food and Drug Administration to collect user fees from industry to support the approval of new drugs and biologics, and is a top priority for this committee.

This was first authorized in 1992, and while there is always room for improvement, the Prescription Drug User Fee Agreement has been a success bringing safe and effective new products to patients in a timelier manner. Every 5 years since, pursuant to a process set forth in statute, Congress has reauthorized the program after reviewing the recommendations from the Food and Drug Administration, industry, patient groups, and other stakeholders.

The committee has been reviewing the Prescription Drug User Fee Agreement since December when it was transmitted to Congress and publicly posted. As I stated in our hearing on the generic

and biosimilar programs earlier this month, Chairman Walden and I are committed to shepherding the user fee legislation through committee following regular order and getting it to the House floor with ample time to spare.

Reauthorization of the user fee agreements every 5 years provides an opportunity, an opportunity to examine, an opportunity to improve upon the state of discovery, development, and delivery of medical therapies in America. For instance, in 2012, the reauthorization of the user fees in the Food and Drug Administration's Safety and Innovation Act established the Breakthrough Therapy Designation. This program expedites the review and approval of promising new drugs that show early evidence of efficacy in serious, life-threatening diseases with an unmet clinical need.

Under this program, over 165 products have been granted breakthrough designation which means more treatments, which means more cures, are being prioritized for patients suffering from some of the most debilitating conditions. I am pleased that the user fee agreements considering now will continue to build upon the success of the Breakthrough Therapy program.

A unique factor in the negotiations of these user fee agreements was its overlap with the development of the 21st Century Cures Act, a bill enacted in December of last year after a multi-Congress effort led by Representative Fred Upton and Representative Diane DeGette. Over the course of the 113th and 114th Congresses, members of this subcommittee worked to uncover opportunities to strengthen and opportunities to streamline the process by which cures are discovered and then made available to patients. The resulting law touches each step of the process through which new treatments come to the bedside.

I am encouraged to see in our witness's testimony that the Prescription Drug User Fee Agreement VI will dedicate resources to complement the implementation of the many priorities, the many priorities of the 21st Century Cures bill. In particular, I like the fact that the FDA will formalize a structure to incorporate patient input and patient experience into the benefit-risk assessment of products that are actually under development. This is a good thing. Patients have the most at stake and they deserve to be heard.

I am also encouraged that the Food and Drug Administration will dedicate resources to modernize clinical trials and evidence development including the utilization of real-world evidence in investment in biomarkers. Real-world evidence has the potential to increase sufficiency and foster robust data collection and analysis. Advancing development of biomarkers has significant promise to accelerate regulatory decision making and expedite the pace of clinical trials without sacrificing standards for efficacy and safety.

Other provisions incorporated into the proposal for PDUFA VI—OK, you made me say it—PDUFA VI. I was trying to just call it the user fee agreements—reflects the top priorities of this committee in the 21st Century Cures Act. Again I want to reiterate my commitment to ensuring that this reauthorization stays on track. We all know there are a lot of competing influences this year, but this year will mark the fifth renewal by Congress, and it is widely agreed that the prescription drug user fee agreements will provide

for the timely review of new drug and new biologic license applications. Again I want to underscore that is a good thing.

I thank all of our witnesses for being here, particularly Dr. Woodcock. Thank you, and welcome again back to our humble little subcommittee for one more hearing. I look forward to hearing from each of you and more about the agreement that is before us today, and I will yield back the balance of my time.

The chair now recognizes the gentleman from Texas, the ranking member of the subcommittee, Gene Green, 5 minutes for an opening statement, please.

[The statement of Mr. Burgess follows:]

PREPARED STATEMENT OF HON. MICHAEL C. BURGESS

The Subcommittee will come to order.

The Chair will recognize himself for an opening statement.

Today's hearing marks the Health Subcommittee's second opportunity to consider the reauthorization of several key FDA user fee programs. The Prescription Drug User Fee Act (PDUFA) authorized FDA to collect user fees from industry to support the approval of new drugs and biologics, and is a top priority for this Committee. It was first authorized in 1992 and, while there is always room for improvement, PDUFA has been a remarkable success, bringing safe and effective new drug products to patients in a more timely manner. Every 5 years since, pursuant to a process set forth in statute, Congress has reauthorized the program after reviewing recommendations from FDA, industry, patient groups, and other stakeholders.

The Committee has been reviewing the PDUFA VI agreement since December, when it was transmitted to Congress and publicly posted. As I stated at our hearing on the generic and biosimilar user fee programs earlier this month, Chairman Walden and I are committed to shepherding the user fee legislation through Committee, following regular order, and getting it to the House floor with ample time to spare.

Reauthorization of the user fee agreements every 5 years provides an opportunity to examine and improve upon the state of discovery, development, and delivery of medical therapies in America. For instance, the 2012 reauthorization of PDUFA in the Food and Drug Administration Safety and Innovation Act, commonly known as FDASIA, established the Breakthrough Therapy Designation. This program expedites the review and approval of promising new drugs that show early evidence of efficacy in serious, life-threatening diseases with unmet clinical need. Under this program over 165 products have been granted breakthrough designation, which means more treatments and cures are being prioritized for patients suffering from some of the most despairing conditions. I am pleased that PDUFA VI will continue to build upon the success of the breakthrough therapy program.

A unique factor in the negotiation of PDUFA VI, was its overlap with development of the 21st Century Cures Act, a bill enacted last year after a multi-year initiative led by Representative Upton and Representative DeGette. Over the course of the 113th and 114th Congresses, members of this subcommittee worked to uncover opportunities to strengthen and streamline the process by which cures are discovered and made available to patients. The resulting law touches each step of the process through which new treatments and cures come to market. I am encouraged to see in our witnesses' testimonies that PDUFA VI will dedicate resources to complement the implementation of many of the priorities in 21st Century Cures.

In particular, I am pleased to see that FDA will formalize a structure to incorporate patient input and experience into the benefit-risk assessment of products in development. Patients have the most at stake, and they deserve to be heard. I am also encouraged to see that FDA will dedicate resources to modernize clinical trials and evidence development, including the utilization of real-world evidence and investment in biomarkers. Real-world evidence has the potential to increase efficiency and foster robust data collection and analysis. Advancing development of biomarkers has incredible promise to accelerate regulatory decision-making and to expedite the pace of clinical trials without sacrificing standards for efficacy and safety.

Numerous other provisions incorporated in the proposal for PDUFA VI reflects the top priorities of this Committee in the 21st Century Cures Act, and I want to reiterate my commitment to ensuring this reauthorization stays on track. This year will mark the fifth renewal by Congress, and it is widely agreed that PDUFA VI will provide for the timely review of new drug and biologic license applications. I

thank our witnesses for being here today and I look forward to hearing more from each of you about the agreement before us today.

**OPENING STATEMENT OF HON. GENE GREEN, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. GREEN. Thank you, Mr. Chairman. I thank all our witnesses, both Dr. Woodcock, welcome back again, and our second panel for being here this morning. Today we are examining the sixth Prescription Drug User Fee Agreement, PDUFA VI. I think it is fair to say that we all support a strong FDA that is responsive to the needs of the patient community and the innovations of scientific research and healthcare delivery.

I am pleased that Congress is moving judicially through the process of reauthorizing the user fee programs and honoring their negotiations that have led to the agreements, and PDUFA is the most mature of the user fee programs having first been enacted in 1992. Sometimes our committee seems like we are a little mature.

The law lays out a detailed process for reauthorization that requires FDA to negotiate with industry to develop recommendations and that the agency solicit public input and hold public hearings and consult with Congress and patients and consumer advocates and other relevant parties. The recommendations that are a result of this process must also be available publicly for a period for public comment, and ultimately are required by statute to be transmitted to Congress.

I was disappointed to see the line in the administration's testimony that they do not stand behind these agreements and hinted towards reopening the painstakingly negotiated products. As we know, we are here today as the result of months of work between FDA and stakeholders to examine the program, figure out what is working and what can work better, and come to an agreement on how the program should be for the next 5 years through a public, drawn-out process.

This process is a long one and the statutory deadline for reauthorization is coming up quickly. Congress has never flirted with neglecting its obligation to reauthorize in a timely and responsible manner. I sincerely hope that this holds true for the sixth reauthorization of PDUFA. Along with the other user fee programs, it must be reauthorized so FDA can do its work and patients maintain access to new therapies without a major disruption in the medical product ecosystem.

PDUFA was first enacted as a way to reduce the time it took FDA to review new drugs and biologics and improve access to medical treatments more quickly. Over the years, the user fees provided under PDUFA have allowed the FDA to hire additional staff and improve the efficiency and predictability of the review process.

Prior to the first PDUFA, the median time for FDA for approval of standard applications was 28 months. Today, the median time for approval for standard applications has been reduced to 12 months, and first-cycle approval rates are at 95 percent. The U.S. remains the gold standard for drug approval and evaluation of safety and efficiency.

The commitment letter for PDUFA VI includes a number of performance goals meant to help the agency with recruiting and re-

taining the scientific and professional staff needed to keep pace with the science. For the first time, PDUFA VI also includes specified agency hiring goals. This builds on the hiring provisions in the 21st Century Cures that will help the agency to compete with the private sector in terms of competitive salary, and gives the agency the authority to hire scientific and technical staff needed to support medical project review.

There have been some that have criticized FDA for being a barrier to the access to innovative new drugs. This is inaccurate. Contrary to the description by the President and others who want to roll back patient safety measures, the FDA's approval process is not slow and burdensome. Today, more than two-thirds of novel drugs are approved first by the FDA rather than anywhere else in the world.

It is clear that PDUFA has been successful in meeting the goal of improving efficiency of the drug review process at FDA and ensuring patients have access to novel therapies. The policies and goals included in the agreements reflect what these stakeholders value and will help ensure advancements and improvements within the FDA and ultimately health care more broadly.

I want to thank the agency and the stakeholders for their leadership on this agreement that will continue the trajectory of patient-centered innovation at the FDA. 21st Century Cures did a great job to advance such reforms and help get new cures from the lab table to the bedside. I look forward to hearing from the FDA and other witnesses on how this agreement will build on these successes and continue to advance the modern, efficient FDA and a healthy pipeline of medical breakthroughs. And I yield back my time.

Mr. GUTHRIE [presiding]. The gentleman yields back his time.

Mr. GREEN. Do we have any other opening statements? No, OK.

Mr. GUTHRIE. We have none on our side. OK, we will turn to the witnesses. We want to thank all of our witnesses for being here today and taking the time to testify before the subcommittee. And each witness will have an opportunity to give an opening statement followed by a round of questions from members.

And we have two panels of witnesses today, and we will begin with our first witness, Dr. Janet Woodcock, Center for Drug Evaluation and Research, Food and Drug Administration. We appreciate you being here. And, Dr. Woodcock, you are now recognized for 5 minutes to give an opening statement.

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

Dr. WOODCOCK. Thank you, and thanks to the members of the subcommittee for inviting me to testify at this important hearing. We are talking here about a program that has been going on for 25 years, the prescription drug user fee program. And as result, as we have already heard, over that time U.S. patients have gone from being one of the last in the world to obtain access to new drugs to in most cases being the first patients in the world who can get access to innovative new therapies, all at the same time maintaining the standards that FDA has for safety and effectiveness of these therapies.

At the same time, we have moved from multiple cycle scenario to predominantly first-cycle approval for these drugs, meaning that the industry and FDA have enough communication, the standards are clear enough, they are able to submit a complete application that can be reviewed and approved without further delay. And this is a great time efficiency and resource efficiency for industry for the FDA and for the medical community alike.

Also, this program has allowed us to accommodate the advances in medical science that have occurred recently over the last several decades. Congress and the U.S. investment in NIH and in biomedical research has caused tremendous growth in scientific understanding. Now we are really contemplating, we have approved drugs for example that are antisense oligonucleotides that act directly on people's DNA. We are looking at multiple applications for gene therapies although none have been approved yet. We are looking at multiple cellular therapies that are under development.

And so this promise that you have been hearing about science is really coming about and we have approved cures for various conditions such as hepatitis C, which has long been a scourge of people.

So the next programmatic proposals, the enhancements for the sixth iteration of this, try to build on the accomplishments that we already have. And as has already been said, the first one is really aligned with the Cures legislation that was passed and that is enhancing the ability to capture patient voice in drug development. Not just on benefit-risks, but patients want to tell us what we should study, what matters to them. What do they want ameliorated about their disease? What is most important? How should we study it?

They want to know, they want to tell us how trials should be designed that work for patients. People always wonder why there is so many dropouts in the trials, missing data. Well, because we designed the trials in a way that patients couldn't participate. So the patient voice is critical, and then at the end of the day how much risk are people willing to trade off in uncertainty for the benefits, the potential benefits of any given therapy. And this will require a rigorous process to generate and develop all these data and bring the patients in, in a rigorous way. It is envisioned in Cures and laid out in Cures, and the programmatic enhancements of PDUFA VI would bolster our ability to do that in a timely manner.

Also, there is support for the Breakthrough Therapy Program. Now what I will say about that is that is probably the first program that has really shortened drug development. As we have all said, drug review isn't the problem. It occurs now in a timely manner, predictable manner, based on PDUFA. But drug development is still a very gnarly problem. It takes too long and it costs too much, right, and there are many failures.

Breakthrough has been the first program as actually drug development time has been shortened, and you have heard that before this committee from a number of witnesses, taking several years off of drug development in the overall time it takes to get those drugs. Part of it is the quality of the compounds, the molecules that are developed under and given breakthrough, but also part of it is the support that FDA is willing to give. And so the new program would give additional resources.

There is also, as was envisioned in Cures, support for biomarker qualification also for the better use of surrogate endpoints, an advancement of clinical trial design, something dear to my heart and I would be happy to talk to you about; advances in the use of real world evidence, which is also a Cures theme; better communication with industry to make sure that we are always on the same page and we move things along; and then administrative improvements including oversight of some of the administrative processes, reports, and financial oversight, to make sure the management and planning of the program is as good as it can be.

So I believe this captures in the programmatic proposals many of the modern themes that need to now address improvements in drug development and drug approval, and I would be happy to answer any questions.

[The prepared statement of Dr. Woodcock follows:]

“Examining FDA’s Prescription Drug User Fee Program”

Testimony of
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

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

March 22, 2017

U.S. Department of Health and Human Services
U.S. Food and Drug Administration
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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to testify today on the sixth authorization of the Prescription Drug User Fee Act (PDUFA), also referred to as “PDUFA VI,” and the Food and Drug Administration’s (FDA or the Agency) efforts to deliver timely access to safe and effective new medications for all Americans.

The PDUFA reauthorization proposal described below was submitted to Congress in December under the previous Administration, and reflects a different approach to the Federal Budget. The Blueprint Budget supports many of the goals of the reauthorization proposal but proposes a different way of financing these goals. The Administration looks forward to working with Congress, with industry input, to develop a reauthorization proposal that speeds the development and approval of vital drugs and biologics 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 premarket 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.

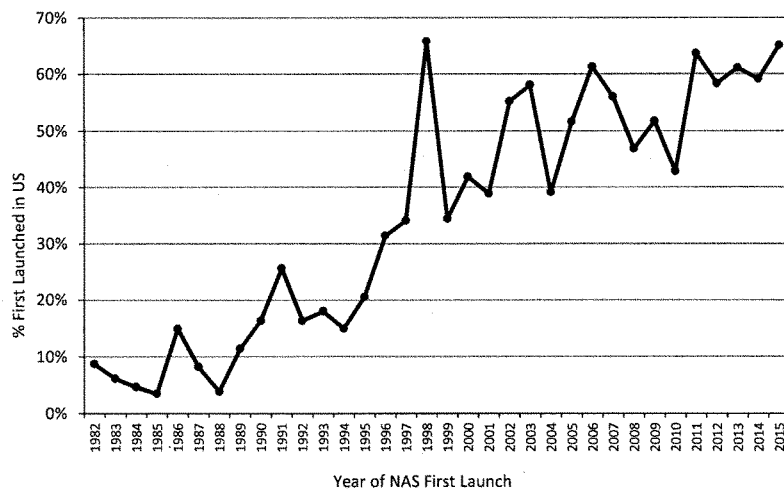
To tackle these challenges, Congress passed PDUFA, which authorized FDA to collect industry user fees to hire additional staff and upgrade its information technology systems. In return, it committed the Agency to speed the application review process for new drugs without compromising its high standards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

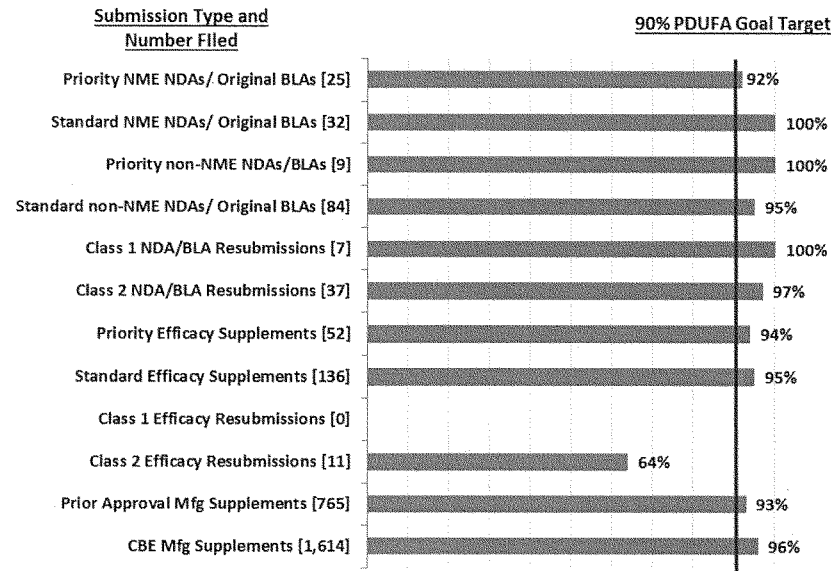


Source: *Scrip Magazine* (1982 - 2006), *Pharmaprojects/Citeline Pharma R&D Annual Review* (2007 - 2016)

The five-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, below.

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

Data as of 9/30/2016

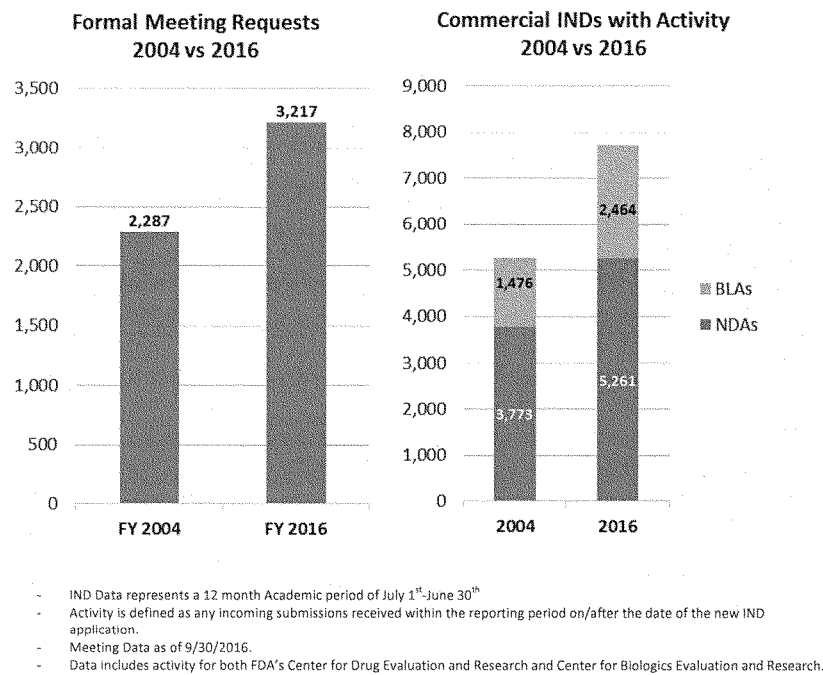
Increasing the Timeliness and Efficiency of Premarket Review

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

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

companies, and the corresponding growth in company requests for development phase meetings with FDA, as shown in Figure 3.

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

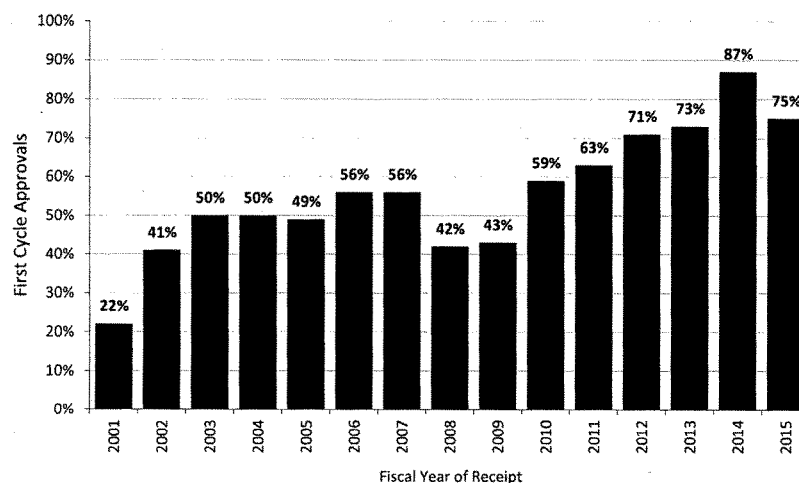


The volume of formal meetings requested by drug sponsors has steadily grown over the course of PDUFA. Early and frequent communication between sponsors and FDA serves to improve the efficiency of drug development. Indeed, it is one of the cornerstones of the Breakthrough Therapy program. FDA-sponsor 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 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 eighty percent (86 percent) were approved first in the United States.

While a standard review is typically completed in ten months, FDA expedites review for priority drugs to be completed within six 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 physician'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 2010-2015. Emergency requests are usually granted immediately over the phone and non-emergencies are processed in a median of four days.

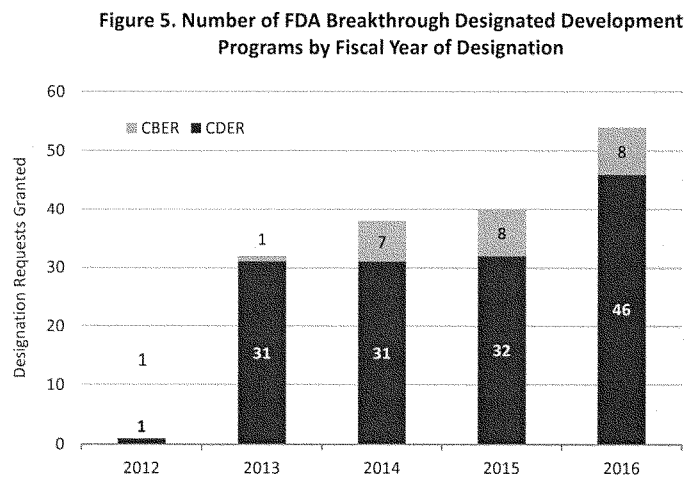
Access to investigational products requires the active cooperation of the treating physician, industry and FDA in order to be successful. In particular, the company developing the investigational product must be willing to provide it – FDA cannot force a company to manufacture a product or to make a 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.



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

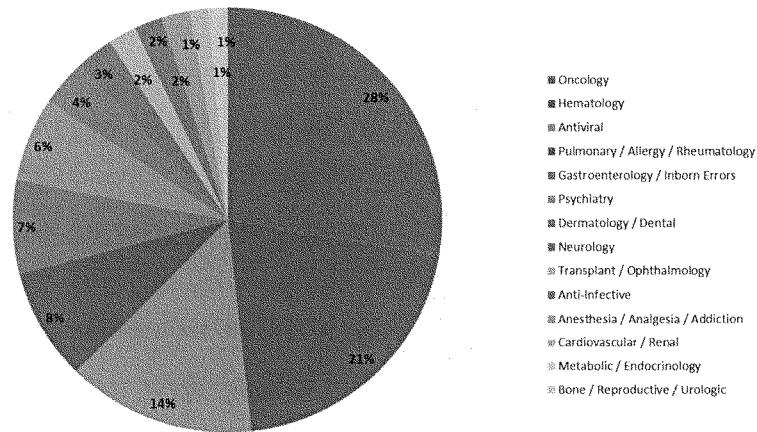
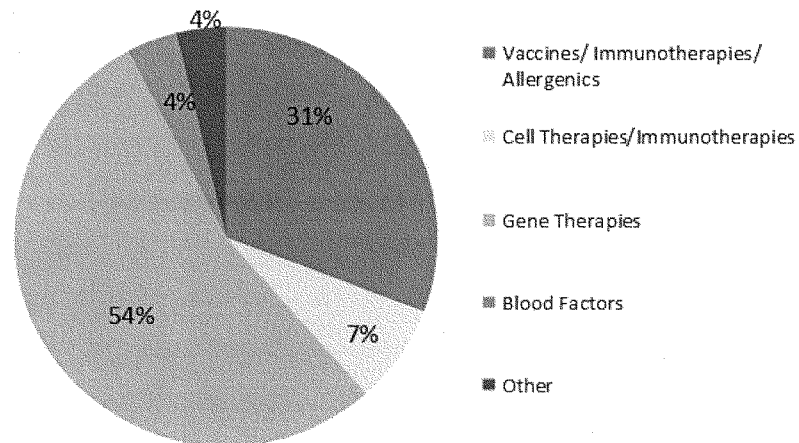


Figure 6b. CBER Breakthrough Therapy Requests Granted by Product Type



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

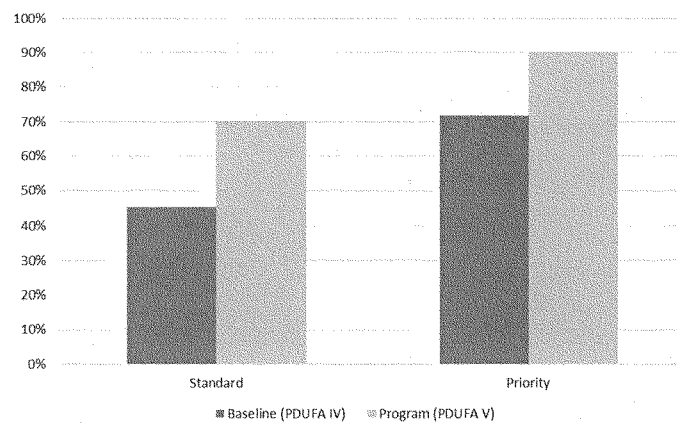
We are currently in the final year of the PDUFA V program. Over the years since the start of PDUFA I in 1992, the complexity of scientific and clinical issues in the study of new drugs has grown, including use of genetic targeting, biomarkers, novel trial designs, plans and programs to ensure effective 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 five 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 decision-making. 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 decision making.

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 decision making. 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 decision making.

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 decision making. 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 decision-making 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 FY 2019, and increase to 90 percent by FY 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 decision making, 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 decision making.

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, a dedicated scientific recruiting function, metric goals for human drug review staff hiring, and 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 five-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.

CONCLUSION

PDUFA has revolutionized the drug review process in the United States, 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 towards 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 drug and biologics 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 will allow FDA to build upon the program's demonstrated success, and in so doing, further benefit patients and affirm our nation's standing as a global leader in biomedical innovation.

Mr. GUTHRIE. Thank you. I want to thank you for your testimony. We will now move to the first Q&A portion of the hearing, and I will begin the questioning and recognize myself for 5 minutes.

So Dr. Woodcock, as part of 21st Century Cures, this committee included provisions that set up FDA Intercenter Institutes of Excellence in major disease areas to improve coordination across the agency. FDA has since established the Oncology Center of Excellence. Can you provide us with an update on how things are going so far and if there is anything we can do to help ensure smooth and timely implementation?

Dr. WOODCOCK. Yes. The Oncology Center of Excellence is considered a joint venture by the three medical products centers, Center for Biologics, Center for Devices and Radiological Health, and Center for Drugs. And so we put this together jointly, it resides up in the office right above us. Dr. Richard Pazdur is the director of that office.

And the procedures that we are running, they will review the clinical oncology, the medical oncology portion of any product that comes in with a medical oncology indication to any of the three centers. So they will do the medical part of that review, and Rick will direct it, but it will include oncologists from Drugs and Biologics as appropriate to that particular cancer area.

So we have worked out the procedures and so forth and we expect those applications then will go before the Oncologic Drugs Advisory Committee and be heard. And then the Center, whichever Center has the product, will complete the rest of the product review which is about the quality of the product and the control of that quality, and then we will actually approve the application using the clinical recommendations from the Oncology Center of Excellence.

And the Center also will be the out-facing, outward facing group that will interact with the medical oncology and patient community.

Mr. GUTHRIE. OK, thank you. I want to yield time to my good friend from Virginia, Mr. Griffith.

Mr. GRIFFITH. Thank you very much. I appreciate that. Dr. Woodcock, prior to the FDA's encouraging the development of abuse deterrent opioids, manufacturers should be incorporating these technologies into their products and testing whether they deter various routes of potential abuse, intranasal, intravenous, et cetera. If they do, manufacturers need to be able to include this data in their product labeling and communicate this useful information to healthcare providers.

I understand a recent exclusivity determination by FDA calls into question whether multiple manufacturers in the same product class could make such claims even if their data justifies it and even if they are using different technologies. Is that accurate?

Dr. WOODCOCK. It is likely accurate. I think like many of the laws governing exclusivity that Congress passed long ago, they certainly didn't foresee some of the situations. And we struggle all the time with trying to figure out how to apply exclusivity fairly and justly to everyone and yet not disadvantage public health goals that we may have.

Mr. GRIFFITH. And so you would agree it probably would discourage a manufacturer if they can't go forward and discuss that; a company or a manufacturer might not invest as much if they think that somebody has beaten them to the punch by a few months. And so what you are recommending, if I understood your previous answer is, is that we probably should take a look at it and change the law?

Dr. WOODCOCK. Well, I can't go that far because of course that is your purview.

Mr. GRIFFITH. Yes, ma'am. Thank you.

Dr. WOODCOCK. But I do believe that times have changed.

Mr. GRIFFITH. Yes, ma'am. I appreciate that. Speaking of product manufacturers being able to share useful scientific data and information about their products with doctors, I understand that some previous leaders at the Department of Health and Human Services would not allow FDA to work with Congress to clarify in a responsible and constitutionally sound manner how manufacturers can communicate truthful and non-misleading off-label information.

Now as you and I were just discussing, I prefer that Congress work with you all to make the rules as opposed to leaving it to the courts to decipher. Will you commit to working with us to set up some clear rules of the road so folks know what they can communicate and what they can't?

Dr. WOODCOCK. Certainly. We will work with the administration, through the administration with you on this issue.

Mr. GRIFFITH. All right, I appreciate that very much.

With that Mr. Chairman, I appreciate the time and I yield back.

Mr. GUTHRIE. I yield back my time and I recognize Mr. Green for 5 minutes to ask questions.

Mr. GREEN. Thank you, Mr. Chairman. And thank you, Dr. Woodcock, again for being here this morning. As I mentioned in my opening statement, I was disappointed to see the line in the administration's testimony that they do not stand behind these agreements and hinted toward a reopening of painstakingly negotiated products. Can you explain to the committee what would happen should Congress fail to reauthorize PDUFA and the other user fees before the statutory deadline in September?

Dr. WOODCOCK. If there is not a reauthorization, we must initiate our reduction in force process where we would prepare to let go of for the Center for Drugs is maybe 70 percent of the staff working on the process of review in new human drugs. And we do have carryover balance within the user fee agreements that we are supposed to hold some money back. In case the program terminates we can, over several months, have an orderly process to let go of the staff. And that we would have to start thinking about that in July because there are complicated personnel rules that have to do with who has to be notified first and so forth.

Mr. GREEN. OK, thank you. There seems to be a misunderstanding about the drug development process. We hear often that new therapies take about 10 years to develop and some seem to think that means the application languishes at the agency for a decade. In fact, the FDA review is the final step in the development process and more efficient than ever.

Can you explain to this committee how PDUFA VI builds on the past successes of the program and helps the agency work with stakeholders to not be a bottleneck but a strong partner in getting these new treatments to patients in need?

Dr. WOODCOCK. Certainly. Obviously we have prioritization programs for breakthrough drugs and for priority drugs where they are reviewed in shorter times. We have gotten some reviews out in 3 months, and a drug approved and on the market after the application is submitted where it is a breakthrough.

So, but that doesn't mean that the development time is short. The development time still is quite long and the failure rate of drugs in development is still very high. Perhaps in some areas nine out of ten drugs that get into human testing fail during human testing at huge cost. So a lot of the efforts we are working on, I believe patient focused drug development, the innovative clinical trials, the surrogate endpoints, and biomarkers, all of which are encompassed in the proposed programmatic changes, will help with this drug development phase and making it as short as possible.

As I said, the Breakthrough Therapy Program has actually worked and some of those development programs in the clinic have only been a couple years, so the time to patients has been shortened dramatically.

Mr. GREEN. Can you explain to this committee how PDUFA VI builds on the successes of the program in the past and helps the agency work with stakeholders to not be a bottleneck but a strong partner in getting new treatments to the patients in need? Or that is my question. OK, let me get to the next one.

Many provisions of the user fee agreements resemble ideas we advanced in Cures, things like biomarker qualification programs, incorporation of the patient perspective in decision making, and the advancement of innovative clinical trials are goals we have shared. I am concerned about the impact that the administration's proposed hiring freeze would have on FDA, and could it be made hard to advance these shared goals?

User fees under PDUFA also assist the FDA in hiring and retaining staff necessary to support the activities associated with review of drug applications. The commitment letter for PDUFA VI includes a number of performance goals meant to help the agency with recruiting and retaining the scientific professional staff needed to keep pace with science. In fact, for the first time, PDUFA VI also includes specific agency hiring goals. This builds off the hiring provisions in the 21st Century Cures.

Can you discuss further how the PDUFA VI will help the FDA to hire and train the scientific technical workforce needed to fulfill the goals agreed to in the commitment letter?

Dr. WOODCOCK. Well, for really the first time, this programmatic proposal in PDUFA VI really focuses on some of the administrative processes and tries to set in place some oversight over hiring and so forth, and some new scientific recruitment staff and so forth that would enable us to hire scientists. As I said, the science has really come along, and so we are talking about really high-tech kind of treatments in humans, such as gene therapy in humans and so forth, and we need the scientific staff that are qualified to evaluate those and make sure they are safe as well as that they work.

Mr. GREEN. Well, my time is almost up. And I know our goal is to make sure you have the resources to do it quicker and not lay in another level of bureaucracy to make it even longer. Thank you, Mr. Chairman.

Mr. GUTHRIE. Thank you. The gentleman yields back. Mr. Upton is recognized for 5 minutes.

Mr. UPTON. Well, thank you, Dr. Woodcock. It is great to see you again, and I know all of us on both sides of the aisle here really appreciated your work and your input from the very beginning on getting 21st Century Cures ultimately to the President. And we knew that by expediting the approval of drugs and devices we were going to need require you all at the FDA to help us and to help chart that course for us and provide the right resources so that you would be able to do your job.

And obviously PDUFA VI is very important, very important. And alarming of course to us, a good message to us is if we don't get it done by summer or show that we have made progress by July and August, certainly by September, that you would actually have to RIF 70 percent of the staff, is quite alarming and ought to serve as turning up the burner for us to get our job done, as we have in the past in a very strong bipartisan way, ultimately getting this bill to the President.

A question for you, Diana DeGette and I sent a letter a couple weeks ago to OMB asking about the federal hiring freeze that the President announced as it relates to the implementation of 21st Century Cures. And of course as you know we came up with off-sets, dollar for dollar matching to help with the half billion dollar increase that we gave for the FDA.

Yesterday, it is my understanding that you told the Senate Health Committee—and I have to again compliment Lamar Alexander and the great work that they did over there. But yesterday you told the Health Committee that the White House did give the FDA permission to move forward with hiring on the select user fee positions needed to implement Cures. I don't know if that is a quote or not, but that is my understanding.

Can you provide some more detail? We have not heard back. It is my understanding we have not heard back from our letter that we sent to the White House, but can you tell us more details about the type of hiring that is going to be needed to implement 21st Century Cures and what guidance you have been able to get from both OMB and the White House and which select user fee positions is the FDA hiring?

Dr. WOODCOCK. Well, I am not in a position to discuss that particularly, I can talk about what programmatic needs there will be. Clearly, the patient focused drug development is going to need different kind of scientists than we have traditionally had. We have had laboratory scientists who are looking in test tubes and doctors who are—we are going to need social scientists and other folks who can actually talk to people and get rigorous evidence about what their needs and preferences are and who can work on instruments, say, patient reported outcome measures and so forth. So that is one category that we don't necessarily have enough of.

In addition, on real-world evidence that is some different types of science that we will need to have people who can analyze that,

big data, and so forth. And interesting, we have already had multiple outside parties approach us who are using real-world evidence in different ways and they want to collaborate with us and we are working with them, some of them in the Oncology Center of Excellence. So we will need data scientists of that sort.

And Breakthrough Therapy, which I know isn't Cures, but will need basically people who in specific disease areas particularly rare diseases. We also commit to integrate rare disease expertise within the review teams where there are rare diseases. We are seeing more and more rare diseases being treated.

So we have very focused needs in specific places for a specific kind of scientist, and I am sure that the Biologic Center with the rise in gene and cell therapy and that more or less explosion and also regenerative medicine, they are going to need specific types of scientific expertise.

Mr. UPTON. Great. Well, thanks again for your work and we look forward to continuing the process as we get this thing done too. I yield back. Thank you, Mr. Chairman.

Mr. GUTHRIE. Thank you. The gentleman yields back and Mr. Schrader is recognized for 5 minutes.

Mr. SCHRADER. Thank you very much, Mr. Chairman, and thanks, Ms. Woodcock, for being here again. Very impressive results; I don't know if it is appropriate, but the graphs that are in your written testimony, I think, are pretty dramatic and you should share those with us when you come in and give your testimony. It would be pretty interesting, I think, for everyone to see that with the work of the committee and follow-through by FDA that the first drug approvals have dramatically increased and it is really pretty impressive. So make sure you show yourself to advantage when you become before us here.

I appreciated these comments on the Breakthrough Therapy Program with regard particularly to new and innovative drugs with unmet needs. We are finding that in the generic area that once again there are unmet needs despite the fact there may have been a product and there is either a sole source or no source alternative. Any thought of how the breakthrough process you are currently using on the brand name side might translate into the generic sphere of development?

Dr. WOODCOCK. Our analysis of the issues with generics is more that, you know, about ten percent of what we call reference drugs, the brand drugs, never get a generic filed to them. And so this seems to be a market phenomenon, competition is only attracted where people think they can make money by competing, and the small source products and so forth.

Now in the generic drug user fee program, the second one that we are proposing, the programmatic enhancements include a program to help with complex generics. And those are ones that actually people might not try to enter the market because it is hard, where, say, you are using an autoinjector or you are using a very complex molecule and so it might be hard.

So there, and we have agreed that we would set up a pre-program similar to kind of like the prescription drug user fee where before they send in the application we have meetings with them and we give them advice and we help them develop their products,

so by the time they get the application in the door it actually could be approvable.

So that would help with those types of products, but the small—

Mr. SCHRADER. I guess where I was going—and that is very good and I think that is outstanding and hopefully a benefit to a lot of the companies out there. But I was going, say we are able to encourage a manufacturer to come to market through a variety of different means. We have a bill, Gus Bilirakis and I are trying to find what is the appropriate way to get and incentivize folks to come to market; make it worth their while as you put it.

But once they are there it would be nice if you used that breakthrough approach that has been so successful to also, you know, hasten things through. And I think to, and help us encourage them to come to market and be successful, if they knew that breakthrough approach was going to be applied that might incentivize things also.

Dr. WOODCOCK. Well, we would be happy to work with you. In medicine we have a saying: First do no harm. And sometimes there are unintended consequences and I think it would be worth discussing, because there is such a commercial hit that the innovators take when they get a generic competition on the market that any provisions that they can sue us about or send us citizen petitions or obstruct a process cause delays, and I believe that needs to be taken into account as you think about incentivizing.

Mr. SCHRADER. We are trying to do that. We have a REMS portion of our bill to try and make sure that it is being used appropriately for safety purposes and not block competition in the market. So we are trying to listen to you and your advice.

Dr. WOODCOCK. We would be happy to work with you in this.

Mr. SCHRADER. Second question on the biomarkers. I think that is a great idea because it takes as you said, many times it takes awhile to get these drugs to market and many of them do fail. And so a lot of the manufacturers want to have some idea if they are on the right track and you want to have some idea if they are on the right track, so early intervention and changing things would be appropriate.

Taking a blood pressure measurement or whatever the appropriate biomarker is, how do you follow through on that as the medication goes through the market, or a product goes through the market, to make sure that number one that the biomarker does turn out to be an accurate reflection of what the drug's ultimate outcome is, and then, once the drug is on the market, how do you go back and reassess the biomarkers to make sure they are actually meaningful indicators for you and for the companies?

Dr. WOODCOCK. We have a program known as Accelerated Approval. For some biomarkers such as blood pressure, their benefit is unequivocal and we don't need to keep proving over and over again that lowering blood pressure keeps you from getting strokes and so forth. We know that. But many other biomarkers are, quote, surrogate endpoints that we aren't a hundred percent sure that they are going to translate into benefit, and therefore we would give an accelerated approval it is called. That is kind of a misnomer, kind of misleading, but what that means is we are approv-

ing us based on the biomarker, but they have to do further studies. They are required to do further studies after approval to show that their drug actually causes clinical benefit.

So you get on the market earlier, that is the accelerated part, but you still have to deliver that proof.

Mr. GUTHRIE. Thanks. The gentleman's time has expired. I will recognize Mr. Lance for 5 minutes for questions.

Mr. LANCE. Thank you very much, Mr. Chairman. It is always good to see you, Doctor. I am encouraged to see that the Rare Diseases Program staff will be integrated into review teams for rare disease development programs to provide unique expertise. Could you please speak to the relationship between PDUFA and 21st Century Cures as it relates to drug development tools such as real-world evidence, complex trial designs, and biomarkers, and the importance of getting the agreement to the President's desk by the end of July?

Dr. WOODCOCK. Certainly. Well, what was negotiated in PDUFA VI bolsters certain aspects of Cures with additional resources, and also would have specific timelines put in place and agreements. Some of those are slightly different, but we can reconcile them all kind of defaulting to whatever the earliest thing we agreed to is, we would do it then, all right.

Mr. LANCE. Yes, Dr. Woodcock.

Dr. WOODCOCK. So, for example, real-world evidence, their guidance and so forth we would put out. 21st Century Cures has a broader qualification process, so it includes patient reported outcomes, clinical outcome assessment, as well as biomarkers, whereas the PDUFA agreement is about biomarkers. However, we are going to put up the same process for everything, the Cures process, which puts in place timelines and obligations on both the submitters and the agency. So we will put that across the board.

We expect, as you all know from our discussions, the biomarkers to be the most difficult part of this, and so the PDUFA gives, envisions more support for the biomarker qualification process.

Mr. LANCE. Thank you. Dr. Woodcock, 21st Century Cures included a provision on combination products and that provision directs the agency to improve coordination between the Device and Drug Centers. Considering both Centers are involved in this process, should there be some coordination between the agreements?

Dr. WOODCOCK. Yes, and actually I believe there is. PDUFA VI provides some resources actually are envisioned for the Device Center, all right, to conduct these reviews. But I am pleased to say under the leadership of Dr. Rachel Sherman, who is deputy commissioner, we have made considerable progress already in combination products. We have put together a council, we have mapped the processes, we have improved the processes, we have developed standardized templates and so forth. So I think we have made a lot of progress already and that these efforts in Cures and in the user fee agreements will enhance that.

Mr. LANCE. Do both Centers receive part of the user fee for combination products?

Dr. WOODCOCK. Yes.

Mr. LANCE. Is that the way it works?

Dr. WOODCOCK. Yes.

Mr. LANCE. And as I understand it, the goal in fiscal year 2019 is 50 percent, when the goal in fiscal year 2021 is 90 percent; is that accurate?

Dr. WOODCOCK. I believe so. That is how we typically structure these goals. If we haven't been keeping track the first year or so we try to find out what our baseline is. It may be 80 percent—we might hope so, OK—and then we ratchet it up after that.

Mr. LANCE. Thank you, Dr. Woodcock.

And Mr. Chairman, I yield back 1 minute, 25 seconds.

Mr. GUTHRIE. The gentleman yields back and Mr. Cárdenas is recognized for 5 minutes for questions.

Mr. CÁRDENAS. OK. I will try to yield back a minute and 25 seconds or more to keep up with the program here. Thank you very much, Mr. Chairman, for holding this hearing.

Dr. Woodcock, what is the significance of September 2017 as far as your professional world goes?

Dr. WOODCOCK. If these various user fee programs are not reauthorized at that time, we must initiate processes to let go of the staff and wind down the program. There is money in all these agreements to do that. There is some money held back.

Mr. CÁRDENAS. Yes, money held back to wind it down—

Dr. WOODCOCK. That is all.

Mr. CÁRDENAS [continuing]. Which only expends over a few more months.

Dr. WOODCOCK. That is correct.

Mr. CÁRDENAS. Are many of the people that would be let go, per se, if we legislatively failed to do our job here, would that—you are talking about jobs, people who are specialists, or what kind of jobs are they?

Dr. WOODCOCK. Most of these are doctors and scientists. They are almost all at the Ph.D. or M.D. level. The physicians are generally some specialists, so we would have nephrologists or people who are specializing in medical imaging, and so hard to find people.

Mr. CÁRDENAS. Is it fair to say that getting so close to September 2017 creates kind of a little bit of nervousness amongst people who are trying to get their work done in such an environment?

Dr. WOODCOCK. Well, what we would expect is the productivity would slow down as we approach the brink, tremendously. This has happened once before where we approached it and we lose staff. Our people are heavily recruited into other jobs and they aren't paid as we have all discussed, they aren't paid as much as private sector. And so I would expect we would start to lose people very early who would leave before they got their notice.

Mr. CÁRDENAS. So to that point, if and when this, it seems to have happened before, the ramping up, once there is a restoration after the fact, isn't the ramping up many times harder than it was in the ramping down?

Dr. WOODCOCK. It is indeed. At least in the New Drugs Program where we need to hire physicians, the last time, and we didn't come to a reduction in force, we just came sort of close to that, it took more than a year for the New Drugs Program to recover its losses, and its recruitment rate was slowed down which it already is slow,

because people have kind of lost faith in the viability of the program.

Mr. CÁRDENAS. And something such as a year of that revamping to just restore back to where it was, doesn't that cause a compounding effect potentially when it comes to the actual work being done going forward not only within the department but in the industry that happens to interact with you?

Dr. WOODCOCK. Well, we would have to prioritize very carefully what work would be done. Public safety would come first, obviously, and we would probably not be able to give all the advice that we would like to give or that people would like to have from us.

Mr. CÁRDENAS. So the stress is—I am interpreting this conversation as there would be stress involved in many ways actually expands beyond the department if in fact we weren't able to timely, in a timely fashion get this restored.

Dr. WOODCOCK. I believe that is very accurate.

Mr. CÁRDENAS. Do our job legislatively by the September '17 deadline.

Dr. WOODCOCK. Yes.

Mr. CÁRDENAS. OK. So briefly, Dr. Woodcock, when it comes to what we have done on 21st Century Cures, and your department is complicit in making sure that we do well with that. But at the same time, when it comes to biomarkers can you please discuss further how PDUFA VI will help with these efforts and what further biomarker development activities PDUFA VI will provide resources for?

Dr. WOODCOCK. Certainly. Both 21st Century Cures and the program envisioned in PDUFA VI both envision more effort going to biomarkers. 21st Century Cures sets up a structured program for what we call regulatory qualification, and what that means is new biomarkers, a different sort, we would tell people, the public, you can use this biomarker to make this decision about patients.

Now that can be a very heavy decision say if it is a safety biomarker. We are saying we are trusting human lives to the results of this biomarker. So there is a lot of scientific work that has to go in to make sure that biomarker is providing reliable information to make that decision.

And so what we are going to do, or are instructed to do under Cures and also under this PDUFA VI, is develop the evidence standards, OK. How much evidence, so everybody understands what kind of evidence you need in order to rely upon a new biomarker, and also then evaluate new nominated biomarkers through the Cures process that was set up against those evidence standards. So we have to do both of these, so we need the kind of scientists who are able to do that sort of work.

Mr. GUTHRIE. OK, thank you. The gentleman's time has expired.

Mr. CÁRDENAS. Thank you, Chairman.

Mr. GUTHRIE. Thank you. I now recognize Mr. Long for 5 minutes for questions.

Mr. LONG. Thank you, Mr. Chairman, and thank you, Dr. Woodcock, for being here today. I would like to spend my time with you discussing a very vulnerable population, one that I personally focused on helping. Every year, nearly 200,000 newborns in the United States are admitted to neonatal intensive care units for

treatment. Due to the numerous challenges and despite current pediatric incentives, the last new drug for this population was approved in 1999.

Last year my colleague on this committee Ben Ray Lujan and I introduced the Promoting Life-Saving New Therapies for Neonates Act and are working to introduce the bill this year. Our bill would create a new incentive model by providing a narrowly targeted, transferable exclusivity voucher to drug sponsors who successfully develop products for neonates.

Do you believe the current pediatric incentives have been successful in stimulating therapy development for newborns?

Dr. WOODCOCK. No, not particularly, I do not.

Mr. LONG. Given the lack of development, can you identify the challenges that you see from a regulatory perspective at FDA as well as research and development challenges for the industry?

Dr. WOODCOCK. Well, I believe that we have taken steps recently along with the American Academy of Pediatrics and others, and our new head of pediatrics at FDA is a neonatologist. And together with her and others we have put together a network of NICUs, because part of the issue is the NICUs did not standardize their treatment protocols and so everyone had a different treatment protocol. So if we were going to ask a developer, a drug developer, to develop a drug in NICUs, every NICU director would want a different protocol.

So the first thing that had to be done was say what is the standard of care in the NICU, in the neonatal intensive care unit, and then you can say what are the biggest unmet medical needs for neonates, and then you can start talking about, OK, do we have a trial network or do we have some type of infrastructure that could actually evaluate a new therapy were it developed? And they are working on doing that internationally which is really good news. So I would be happy to update you on the progress on that.

Mr. LONG. This is a tough population to test drugs on.

Dr. WOODCOCK. That is right.

Mr. LONG. Are there steps you believe we could take in the upcoming user fee process to help spur much needed development for this vulnerable patient population?

Dr. WOODCOCK. I don't know in user fee process. My belief is, and I have talked to the American Academy of Pediatrics about this, that the heads of neonatal intensive care units need to get their program together, decide what the standard of care is, decide what the unmet medical needs are, develop trial structures so they could test new drugs, and if they make—if you build it they will come, in my opinion. If you make a pathway clear that developers could use, then I believe they will develop products for neonates, sick neonates. And I believe it is needed.

Mr. LONG. OK, thank you. And once again thank you for being here today taking your time to be with us.

And Mr. Chairman, I yield back.

Mr. GUTHRIE. The gentleman yields back. Ms. Matsui is recognized for 5 minutes for questions.

Ms. MATSUI. Thank you, Mr. Chairman.

Thank you, Dr. Woodcock, for being here. It is wonderful to have you here. First of all, I want to mention that I am concerned with

the President's budget proposal and how it might impact the work that this committee is doing to reauthorize these vital agreements that they have. And I don't think it would be wise to renegotiate the user fee agreements that FDA and the industry have worked so hard to reach, nor do I think it would be wise to impose drastic cuts to the agency's budget authority that would endanger the FDA's ability to collect these user fees. FDA performs many critical functions to keep our food and drugs safe and we cannot afford to compromise that.

Now I am particularly concerned about both the development and the final price of drugs for patients with rare diseases. These populations are often neglected and left with little or no treatments or cures. I want to ensure that we take advantage of our robust research efforts in this country for these rare disease patients.

I am pleased that there are many provisions in the negotiated PDUFA agreement that would make important advances for this rare disease community, particularly building on the effort to include the patient experience in drug development ensuring that staff at FDA who have expertise in rare disease are integrated across different centers.

Dr. Woodcock, can you elaborate on the provisions in PDUFA that would help patients with rare diseases?

Dr. WOODCOCK. Well, I believe the biggest help is actually going to be in the patient focused drug development. And why is that, because rare diseases often are so rare there are not any doctors who really know what happens to the people. And so what we are encouraging and we are seeing now is the patients are getting together and they are having their own patient focused drug development meetings.

They are collecting, and we have given some grants out to help with this, they are collecting natural history on their disease so people actually know what happens to someone with the rare disease. Often it is very disparate. Not everyone with that rare disease has the exact same course, so then it is even harder to study them.

So we are encouraging them to develop natural history so we can help with trial designs and then maybe even outcome measures, like what is the most burdensome part of the disease? What would they like ameliorated? So that then if a company comes along and wants to develop they have a pathway to develop. So that is all baked into these agreements in rigorous ways of collecting that information and helping patient groups so they can develop these things.

But also of course there is an agreement to integrate rare disease staff into review teams so that there is more, it is not all about blood pressure meds and gigantic trials and heart disease, OK, it is about people who have the very rare diseases pose different problems in development.

Ms. MATSUI. Right. OK, can you talk more about the Breakthrough Therapy Program and what successes had it had and what additional resources help FDA with approval of innovative orphan therapies?

Dr. WOODCOCK. Well, we were completely surprised after the Breakthrough provisions were passed that we got so many applica-

tions, all right, and so it has been extremely successful in getting designations. We are only supposed to designate drugs that preliminary data, their early data they develop in the clinic shows it may be a game changer in the disease. It may change the disease; it isn't proven yet.

I can get back to you with the actual numbers, but we have designated hundreds of these to our surprise—we thought it would only be a handful—and we have approved many. And so this is great news for patients, because many times when we approve these they actually are a game changer for that disease.

Ms. MATSUI. OK. That is wonderful. You testified that surrogate endpoints have been the basis for 60 percent of rare disease approvals. Can you explain surrogate endpoints in laymen's terms and why they are important for rare disease approvals?

Dr. WOODCOCK. Surrogate endpoints are something other than how a patient feels or functions or how long they live. So that is our gold standard for approval, it makes you feel better or makes you function better or it makes you live longer. But often diseases take a really long time, OK, to have their manifestations. And say for diseases where you are missing an enzyme—that is many rare diseases. So you are missing an enzyme and you start accumulating that substance inside your body instead of eliminating it.

Ms. MATSUI. Right.

Dr. WOODCOCK. And we can give back these enzymes now, so sometimes we have accepted the fact that in vital organs that material goes away, all right. Well, that has to be really good news. It is not a hundred percent sure that doing that will reverse the symptoms of the disease, but it is pretty plausible, right? So often we give an accelerated approval like we were talking about saying, OK, we will get it on the market. All the patients can start taking this because is it removing this stuff from the body, but we want you to show with a registry or other that actually they are feeling better eventually, to make sure that is the truth.

Ms. MATSUI. OK. Thank you very much, and I have gone past my time and I yield back.

Mr. GUTHRIE. Thank you. The time has expired, and we recognize Mr. Bilirakis for 5 minutes for questions.

Mr. BILIRAKIS. Thank you so much. I appreciate it, Mr. Chairman. And thank you, Dr. Woodcock, for coming today again.

Recently the FDA issued a request for comment on a proposed Office of Patient Affairs. Can you tell us what the goal of this office is, how it fits into the agency with its current patient related programs, and how this office would benefit patients?

Dr. WOODCOCK. The thought is that many patients don't understand the structure of FDA. FDA has long been divided into Centers, and if you are kind of inside Washington, you know you call the Biologic Center and you call the Drug Center. But what do you do if you don't know even who to call, right. So the thought is for medical products, not for foods or whatever, but for medical products, if people have questions about medical products there ought to be a little bit of a front-facing, patient-facing unit that can help people figure out who to ask the question. And so that is, I think, a lot of the rationale behind it.

Mr. BILIRAKIS. All right, thank you. Dr. Woodcock, in the 21st Century Cures Act we were able to pass reform language to modernize the Office of Combination Products. As you know, combination products are products on the market that have elements of a medical device and a drug, like inhalers and insulin injectors. Many patients need and rely on combination products, as you know.

While we worked on the 21st Century Cures, I asked FDA about innovation in the drug and device space as more and more innovative products may be combination products. At the time there were complaints from innovators about the slow and burdensome FDA process for approving combination products. One of your colleagues at FDA stated in an hearing, "That is a place that does require probably further discussion and whether or not there are changes to be thought about to make that intersection work better than it currently does."

Can you update us on what the FDA is doing on the drug side to implement the Cures language for combination products and what was agreed to in the user fee agreement?

Dr. WOODCOCK. Certainly. Well, what we are doing, the Cures product calls for work on this and the user fee program, the drug user fee program, actually provides resources for review of the device portion, OK, so that has been agreed to. But in advance of that we have set up a combination product council at the agency. We have mapped the different processes. We have revised them to make them more efficient. We are tracking them. We have standard forms and so forth, and I think everyone agrees that that is all going much better now.

So even in advance of implementing these we have gotten sort of the basics down about how to do these reviews more effectively given that we agree with you, this is the future of products. But the PDUFA program proposes that more resources be given to the Device Center to conduct these reviews of drug related, drug-led combination products of which many of these are.

Mr. BILIRAKIS. OK, very good. I yield back, Mr. Chairman. Thank you.

Mr. GUTHRIE. The gentleman yields back, and Ms. Eshoo is recognized for 5 minutes for questions.

Ms. ESHOO. Thank you, Mr. Chairman. Welcome, Dr. Woodcock.

Dr. WOODCOCK. Thank you.

Ms. ESHOO. It is always good to see you. Mr. Long is not here, but I wanted to say for the record that in FDASIA when we built that and passed it, I had language in that that required neonatologists being hired, and that was back in 2012. So I will talk to him later. I will be happy to work with him, but I think that that is important to set down for the record.

The PDUFA was enacted in 1992. I was running for Congress when that was put into place. And at that time drug review times were lagging and the FDA simply really couldn't keep up with the flood of new drug applications. So through these user fees paid by applicants it has given the FDA the resources it needed to hire and support more staff very specifically to move the applications forward.

I think the program overall has been successful at reducing review time backlogs, and even though the President criticized the FDA during his joint address to the Congress for, "having a slow and burdensome approval process," I think the facts really dispute that claim. And we are always looking to improve it, but it has been instrumental in promoting the improvements we have seen over the past 25 years.

Now I want to talk about two bills that I authored. I am very proud of them. One the BPCA, the Best Pharmaceuticals for Children Act; and the other, PREA, the Pediatric Research Equity Act. Both of these programs were permanently reauthorized in 2012, but I think today we need some improvements. We know that children are not just small adults; that drugs work differently in them than in adults and they have to be studied specifically for their use. That is why I authored both of these pieces of legislation. I think they have a track record of success, because more than 664 drug labels have been revised with important pediatric information as a result of the two bills.

So my question to you, Dr. Woodcock, is what is the implication of the orphan drug exemption in PREA on children's health? Are there examples of orphan drugs that would have benefited from a pediatric study but were not studied as a result of the orphan drug exemption in PREA?

Dr. WOODCOCK. I have to get back to you on specifics, are there any. In general, the orphan diseases, the rare diseases are sort of throughout life. Many of them start in childhood and so children are usually studied.

So much of the pediatric drug development problems were the fact that drugs were studied for adult diseases and there would be a few children who had them, relatively speaking, and they weren't ever studied, right, and it was used off-label in them, but in many of the rare diseases that rare disease starts in childhood and continues through.

But there may be some instances, and we can get back to you about where the rare disease predominates in adults. There are only a few children, and perhaps then the exemption means that those children may not be studied, but in talking to the rare disease and the orphan staff and the pediatric staff they don't believe this is a large problem.

Ms. ESHOO. Well, orphan drugs are, as you know they are currently exempt from PREA's—

Dr. WOODCOCK. Yes.

Ms. ESHOO [continuing]. Pediatric study requirements and that is why I am asking about it. Before the BPCA and PREA, the vast majority of drugs, more than 80 percent used in children were used off-label and without data on their safety or efficacy, and today that number has been reduced to approximately 50 percent, but that is still a lot. That is still a lot.

Why, if FDA has the authority to issue civil monetary penalties for other violations of the Food, Drug, and Cosmetic Act, including violations of post-marketing requirements, do you think that the FDA should be prohibited from using that authority to ensure compliance with PREA post-marketing requirements?

Dr. WOODCOCK. That is a legal question and we would be happy to work with you and get back to you on that.

Ms. ESHOO. But do you have any thoughts on it? You deal with legal all the time.

Dr. WOODCOCK. I do.

Ms. ESHOO. You live within a legal framework.

Dr. WOODCOCK. That is correct. The civil money penalties provisions and those provisions are apparently rather difficult to operate and implement, but so I would prefer getting back to you with the agencies.

Ms. ESHOO. Sure. That is fine. Thank you very much.

Thank you, Mr. Chairman.

Mr. GUTHRIE. Thank you. The lady yields back, and I now recognize Mrs. Blackburn for 5 minutes for asking questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

Dr. Woodcock, you were so patient to come to us regularly, and we do appreciate it because we are so interested in making certain that things that are supposed to be done are tended to.

As Chairman Upton mentioned, 21st Century Cures, the implementation there, of course the Children Count Act which I had had that component, that is something that we are going to watch very closely and so we do appreciate the updates. We know it takes a lot of time to come up here, but we are very appreciative. I just want to quickly look at the abuse deterrent opioids and the components that are there. March 2016, you did the draft guidance. When is there going to be the final guidance on that? What is the expectation?

And then I want to know, I know we have touched around the edges on this, but talk a little bit about the actions that can and should be taken from you all to advance the abuse deterrent opioids and to get these into the marketplace, just a little bit there. And that is really my only two questions.

Dr. WOODCOCK. Certainly. Well, as far as the guidance, it is very difficult ever to give a firm date certain when a final is going to come out.

Mrs. BLACKBURN. Just an expectation or timeline.

Dr. WOODCOCK. Well, let me just assure you that we are putting great effort into this, because really what we need to do, we think, is incentivize innovator development of various abuse deterrent formulations. The current ones, as we have already discussed, are kind of version 1.0 and surely we can do better, right. And so there has to be probably some incentives there.

And then generics, we need a pathway so that the generics understand what they would have to do to show that they source exactly the same as the innovator, because uptake of these abuse deterrent formulations is lower because there are a lot of old opioids on the market that are very inexpensive that are not abuse deterrent.

And that is often for health systems the preferred opioid to use to save money, so we need a progression of incentives and also a clear pathway. But the innovation needs to go from the innovators, the people who are out there trying to figure out better ways to deter abuse.

Mrs. BLACKBURN. Right, but are we talking 6 months, a year? I mean, when do you think there will be a final decision——

Dr. WOODCOCK. A final guidance for the generic?

Mrs. BLACKBURN. Yes.

Dr. WOODCOCK. I would hope within 6 months, I certainly would.

Mrs. BLACKBURN. That is great. And then if you will speak just a little bit toward what further the FDA can do to spur the abuse deterrent opioids.

Dr. WOODCOCK. Sure. There are many things we are trying to do, one of them though is trying to incentivize development of drugs, new drugs that don't have these abuse liabilities to treat pain, and we have approved a number of them. They are often for specific conditions.

For example, we approved one for neuropathic pain and that is now being used by the neurologist, those drugs, instead of opioids because opioids aren't very good for neuropathic pain. So that cuts out one category of people who are getting these opioids.

So we want to stimulate and we have been working on this for years with the outside world, scientific world, trying to stimulate the development of drugs that aren't opioids that don't have these abuse liabilities, because people are going to continue prescribing opioids for people in pain unless they have something else to offer. So also we have workshops and we work on abuse deterrent formulations to try and stimulate and work with innovators on new ways to deter abuse.

Mr. GRIFFITH. The gentlelady yields back. Mr. Butterfield is recognized for 5 minutes for questions.

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

Let me just begin by thanking you and Dr. Woodcock, for coming back. You have been at that table many times and thank you so very much. Chairman Burgess, who is not here today, but I want to thank him for holding this hearing on the Prescription Drug User Fee Agreement reauthorization.

Since I came to Congress some 12 years ago back in '04, Congress has come together under the leadership of both Democrats and Republicans to pass this important bipartisan legislation. Just last year we passed the 21st Century Cures Act that this committee drafted and passed unanimously to help boost the resources of the Food and Drug Administration and encourage the development of new treatments.

For my constituents in North Carolina, developing new treatments can literally make the difference between life and death. Health outcomes for many in the communities that I represent are deeply concerning. Many of my constituents are African American citizens. By most measurable health statistics, outcomes for African Americans lag far behind. Supporting the reauthorization of PDUFA is important to finding new treatments to help reduce health disparities for my constituents and indeed Americans all across the country.

Through additional resources made possible by PDUFA V, the FDA has been able to work with industry to make available new treatments for rare diseases through the Breakthrough Therapy Program. Through November of last year, FDA has granted, I am told, 165 breakthrough therapy requests. This includes treatment

in many areas that disproportionately impact my constituents and African Americans throughout the country.

Breakthrough designations have been granted for diseases like HIV and hepatitis C, and colorectal cancer, all of which impact minorities at high rates. PDUFA VI has the potential to make advancements in areas from breakthrough therapies and real-world evidence to clinical trials and biomarkers. The additional resources made possible through the proposed new fee structure can help FDA build the workforce needed to complete these new tasks.

However, this administration's executive actions and proposed budget do not seem to understand the importance of FDA's mission to help patients and improve public health. The impact of a hiring freeze on the FDA implemented by the Trump administration is still unclear. Also the administration's budget proposal fails to understand the good-faith effort that has been put forth by the FDA and by industry and patient advocacy groups all working together. Now is the time to come together to support the FDA. Our constituents are counting on us, my colleagues, to work together in this space.

Dr. Woodcock, I am excited by the innovations occurring in cancer drug development as cancer drugs are now being developed by molecular target. By identifying the drivers of the cancers, these new molecularly targeted drugs are achieving great new strides in treatment and providing greater health to cancer patients. These targeted drugs are often effective for many types of cancers.

Question, are innovative new cancer treatments for adults also tested for children with the same targets as adult cancers?

Dr. WOODCOCK. Not generally. The paradigm is changing and typically over time treatments for cancer as well as other disorders have been according to disease. So in cancer it is what we call histology, which basically means the organ that the cancer originated in. That is why we call it colon cancer or we call it whatever cancer, lung cancer, right.

But these molecular alterations may go across diseases and it may be only a small subset of each of these cancers are driven by the same molecular alteration. That isn't something that has really been looked at very closely in children. It may be that there are rare mutations in children that are the similar as the mutation in adult for these molecular targeted therapies.

Mr. BUTTERFIELD. OK. Also my colleague Representative McCaul of Texas and I introduced the RACE for Children Act, H.R. 1231, to promote the discovery of new cures for children with cancer. First, the RACE for Children Act would provide that a drug company will provide a pediatric study plan of a drug pursuant to the Pediatric Research Equity Act if the drug is, "intended for the treatment of an adult cancer and is directed at a molecular target considered to be germane to the growth and progression of such pediatric cancer."

Do you believe this provision would create greater access to novel cancer drugs for pediatric cancer research?

Dr. WOODCOCK. I am not able to comment on that at this time, but we would be happy to work with you on this.

Mr. BUTTERFIELD. All right. We are deep into this and we would like all the help we can get. Secondly, the RACE for Children Act would end the—I am over, yes. I yield back.

Mr. GUTHRIE. I yield back. Thank you for yielding back. I see no questions on the majority side. Mr. Sarbanes, you are recognized for 5 minutes for questions.

Mr. SARBANES. Thank you, Mr. Chairman.

Thank you, Dr. Woodcock, for joining us. I have been here 10 years, I think on four or five different committees. You are my all-time favorite witness. I just want you to know that. Because you are so professional in your presentations, so knowledgeable, and you play things straight, so I appreciate your being here.

I am fascinated by this idea of including, incorporating real-world evidence in regulatory decision making. I mean the implications of it are kind of humorous because it suggests that up until now there hasn't been real-world evidence in the process, but I certainly understand what it is meant to convey.

And I was wondering if you would just talk a little bit about that topic. And obviously the agency is going to have to come up with, and I know you are in the process of doing this, a kind of formal process for identifying what qualifies as real-world evidence and then how it gets gathered and then how it gets translated back to the agency, how much weight is given to it as part of the overall analysis that is done by the staff there at the FDA. So if you could maybe just talk about that a little bit more that would be helpful.

Dr. WOODCOCK. Certainly. Well, FDA runs actually one of the largest real-world evidence gathering operations that is around in the health area, which is our Sentinel System, which is for drug safety and was mandated by Congress. And there we have 193 million different people's claims data that we can access, all right, anonymously, and we use that for drug safety analysis.

And the Congress told us that that should be used first rather than requiring companies perhaps to do specific observational studies. And recently, as we have institutionalized this system there are four programs where we are able to do something in Sentinel and not require additional outside studies, but that is safety.

Now on the effectiveness side, obviously you would only collect real-world data if the drug were on the market, OK, because before a drug gets on the market data is collected into clinical trials, it is not just collected into doctor's offices. So that would be after a drug is marketed can we collect patient experience data to perhaps broaden the indication or add new indications or whatever.

Mr. SARBANES. Can you comment on how sort of off-label use relates to that?

Dr. WOODCOCK. Well, it does relate to it, because often, for example, let's take these oncology drugs and these targeted drugs. So they target a specific target. We may approve it for a number of tumors, but then there may be somebody who comes in and they have a rare tumor or a tumor that this is an unusual type and they have that mutation. So the physician may treat them with the targeted agent and that would be considered off-label use although it is completely rational, right.

So what we are working with a large number of outside parties who are gathering this information up in different ways and then

they want to collect that experience of the patients, those rare patients, and then perhaps if they responded and we can document that then maybe we can add that to the label and say if you have a rare patient like this come in they should be treated with this targeted therapy too. So that is an example.

There also are registries, and some people consider those real-world evidence and some don't. But we are trying to put registries together, get that registry information, make sure it is——

Mr. SARBANES. Just on that point again intrigued me. What would make certain people consider a registry real-world evidence and other people not consider it real-world evidence?

Dr. WOODCOCK. Yes. Well, some people are sort of purists and they consider real-world evidence only collected like in the course of ordinary medical care and of stock, OK. Other people consider it evidence that is collected during the course of treatment even if you add a few bells and whistles. So we really don't care. This is evidence outside of standard clinical trials, so let's figure out for all of it what can we do to gather more information about performance of drugs outside of your traditional clinical trial.

Mr. SARBANES. Would you imagine that at the end of this process adding this to your portfolio, if you want to call it that, that there would be maybe some kind of advisory council or group that the FDA would bring into the process of identifying real-world evidence? I mean, what kind of structures do you think we might see, or is it premature to——

Dr. WOODCOCK. I think what you would see is a series of policy sort of guidances or pronouncements by the FDA as we are able to broaden our uses of and examples of how we have used it. And in some of those cases we may take it to a specific advisory committee, say we think we should add these, say, tumors to the label because here is the real-world experience and it looks like these people respond and they would never get in a clinical trial because they are rare or whatever.

So that I think is the kind of accumulating information. We can't just have people sort of think great thoughts absent examples of what can be done.

Mr. SARBANES. Right, thanks very much. I yield back.

Mr. GUTHRIE. Yes, thanks, time has expired. And seeing no other members here to ask questions—well, thank you, Dr. Woodcock, for being here. I concur it is always great to have you here and you always do a good job. I appreciate it.

Dr. WOODCOCK. Thank you.

Mr. GUTHRIE. We will now transition to our second panel.

Thank you. We want to thank all of the witnesses for being here today and taking the time to testify before the subcommittee. As a reminder, each witness will have the opportunity to give an opening statement followed by a round of questions for members.

Our second panel of witnesses includes Mr. Jeff Allen, President and CEO, Friends of Cancer Research; Ms. Kay Holcombe, Senior Vice President of Science Policy, Biotechnology Industry Organization; and Dr. Anne Pritchett, Vice President of Policy and Research, Pharmaceutical Research and Manufacturers of America.

We appreciate you all being here, and we will begin the panel with Mr. Allen, and you are now recognized for 5 minutes for an opening statement.

STATEMENTS OF JEFF ALLEN, PHD, PRESIDENT AND CEO, FRIENDS OF CANCER RESEARCH; KAY HOLCOMBE, SENIOR VICE PRESIDENT OF SCIENCE POLICY, BIOTECHNOLOGY INDUSTRY ORGANIZATION; AND, ANNE PRITCHETT, PHD, VICE PRESIDENT OF POLICY AND RESEARCH, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

STATEMENT OF JEFF ALLEN

Mr. ALLEN. Good morning, Vice Chairman Guthrie, Ranking Member Green, and members of the subcommittee. It is an honor to be here today to provide the perspective of Friends of Cancer Research. The current pace of scientific discovery represents an unparalleled opportunity to improve human health. The critical component to this is an FDA that is highly responsive to public health needs and able to evolve with cutting edge science.

Prior to the initial user fee authorization in 1992, patients in other parts of the world were gaining access to new medicines more readily than Americans with only about ten percent of new treatments reaching U.S. patients first. Today that paradigm has been reversed. Funds through the PDUFA mechanism have allowed the FDA to make the review process more predictable, efficient, and accessible. In fact, our data indicates that for new cancer drugs approved by both the FDA and the European counterpart, 97 percent were available in the United States first. Furthermore, the FDA approved them on average nearly 6 months faster.

This sixth authorization of the user fee agreement comes at a critical time for the agency and for patients. It will support numerous initiatives, a couple of which I would like to mention today. PDUFA VI advances the role of patients and their experiences. PDUFA V, in the 21st Century Cures Act, provided important steps to incorporate the patient perspective in drug development.

The PDUFA VI agreement will further assist organizations, researchers, in collecting patient experience data, create channels for providing such data to the FDA, and it will help develop methods for analyzing it. PDUFA VI supports the Breakthrough Therapy Designation. This designation to expedite the development of highly promising new drugs has been rapidly implemented. To date, 170 designations have been granted leading to 79 approvals.

Upon examining the pre-market development time of new cancer drugs, we found that it was over 2 years shorter for breakthrough designated drugs than for those without the designation. PDUFA VI will provide resources necessary for continued success. PDUFA VI promotes qualification and use of drug development tools that can help identify patients for which a drug is likely to work, offer early indicators of toxicity to help improve patient safety, and in some cases indicate that a drug will have long term benefit. The agreement will help create a process in which new tools can be accurately assessed and ensure their appropriate use.

PDUFA VI enhances the use of real-world evidence. Once a drug reaches real-world populations there may be unanswered questions

about its effects, particularly in patients not represented in clinical trials. The collection of real-world evidence allows for a greater understanding of drugs currently in use. By allocating user fee funding toward these programs, the FDA and other stakeholders will be able to identify limitations and explore different opportunities for the use of data collected from post-market experience.

To that end, FDA approved labels should be a vitally important source of information to guide the safe and effective use of prescription drugs. However, in some instances, such as drugs that have gone off patent, labels may have become outdated and no longer reflect optimal use. This is illustrated by extensive discrepancies between FDA approved labels and widely accepted practice guidelines.

The FDA could play a greater role in evaluating the relevant data to update the product label as appropriate and adjudicate between the uses backed by strong evidence and those backed by less persuasive information. This would establish a high standard for post-market evidence and make the product labels more useful. For the programs of this proposed user fee agreement to succeed, the full budget of the FDA must be robust and the capacity of which the agency can maintain and hire the best scientific minds must be unencumbered.

Despite opportunities afforded by PDUFA VI, the passage of the 21st Century Cures Act, and the enormous contributions of this committee, I would be remiss to state that the FDA and the people who rely on it are optimally positioned at present. The proposed cuts to biomedical research will put the brakes on the engines of discovery and jeopardize the development of new medicines for patients. Holding the FDA budget authority at stagnant levels prevents progress on agency functions that are not covered by user fees.

Among the challenges that have been exacerbated in the current environment is the implementation of the FDA Oncology Center for Excellence, an innovative approach and a new model for collaboration. The potential of a detrimental budget and the presence of the current hiring freeze put the OCE and so many other transformational opportunities at significant risk. For the people who currently depend on safe and effective medicines, for those who are holding strong for the breakthroughs to come, and for every future patient, there isn't time to waste. We urge Congress to swiftly pass the sixth reauthorization of PDUFA. Thank you.

[The prepared statement of Jeff Allen follows:]



Examining FDA's Prescription Drug User Fee Program

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

Jeff Allen, PhD
President & CEO
Friends of Cancer Research

March 22, 2017

Examining FDA's Prescription Drug User Fee Program

Testimony of Jeff Allen, PhD, President & CEO, Friends of Cancer Research

Few in biomedical science can recall a time of greater scientific progress. Hardly a day goes by without reports of a new medical breakthrough, a new partnership to drive discovery forward, or a new milestone toward addressing a previously untreatable disease. This pace of scientific discovery represents an unparalleled opportunity to improve human health. While it offers great hope for the future, progress has not been universal, and significant challenges remain. In the field of oncology, certain types of cancer are no longer the deadly diseases they once were, but instead are much like chronic conditions that can be effectively managed for a lifetime. But other types of cancer have not seen a new treatment for decades, if at all, leaving some to wonder if they will ever reap the benefits of progress.

The drugs and biologics being developed today to treat many diseases are far more effective than their predecessors, but they're also more complex. Even for some of the most notable new advancements benefit only a subset of patients. This additional complexity adds to the process of developing a new medicines, which already reportedly takes upwards of 12 years and costs over \$1 billion.¹ But together we have the opportunity to support breakthrough science, design systems that can surmount new challenges, and pave the way for new discoveries to reach the people who need them most. I, and millions of people across this country, hope that the work of this committee will be a catalyst to accelerate getting the right medicines to the right patients at the right time.

¹ Adams, C. P. and Brantner, V. V. Health Economics, 19 (2010), 130–141. doi: 10.1002/hec.1454

A critical component to achieving this goal is a well-resourced, accessible, and scientifically-oriented Food & Drug Administration (FDA). The FDA continues to be an agency that is highly responsive to public health needs and evolves with cutting edge science. It is able to do so, in part, because of the Prescription Drug User Fee Act (PDUFA).

The Prescription Drug User Fee Act

PDUFA was first passed in 1992 to alleviate a backlog of new drug applications. Prior to the initial user-fee authorizations, patients in other parts of the world were gaining access to new medicines more readily than Americans, with only about 10% of new treatments reaching U.S. patients first.² Today, that paradigm has largely been reversed. Funds provided through the PDUFA mechanism have allowed the FDA to clear the backlog of applications and have made the review process more predictable, efficient, and accessible. As a result, patients in this country have gained timely access to new medicines. In fact, in a study that we first published in *Health Affairs*,³ we examined the review times for new oncology drugs by the FDA and its European counterpart, the European Medicines Agency (EMA). Between the years 2003 and 2016, 73 new cancer drugs were approved by both the FDA and EMA. Of those drugs, 97% (71 of 73) were available in the U.S. before Europe. Furthermore, the FDA approved new cancer drugs on average nearly 6 months faster than the EMA (Fig. 1). Other research groups have also demonstrated that FDA regularly approves products faster than other global regulatory agencies and that this is the case for all drug reviews, not just for oncology drugs.⁴

² Hearing of the Committee on Health, Education, Labor, and Pensions, US Senate: FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients. 112th Congress. March 29, 2012. <https://www.gpo.gov/fdsys/pkg/CHRG-112shrg90814/html/CHRG-112shrg90814.htm> Accessed 3.17.17

³ Roberts S, Allen J, and Sigal E. *Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe*. *Health Aff* July 2011 vol. 30 no. 7 1375-1381: <http://content.healthaffairs.org/content/30/7/1375.full.html> Accessed 3.17.17

⁴ Downing NS, Aminawung JA, Shah ND, Braunstein JB, M.D., Krumholz HM, Ross JS. *Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies*. *N Engl J Med* 2012; 366:2284-2293: <http://www.nejm.org/doi/full/10.1056/NEJMsa1200223#t=article> Accessed 3.17.17

Figure 1. Comparison of FDA and EMA Review of New Oncology Drugs (2003-2016)

Drugs Approved by FDA and EMA n=73		
	FDA	EMA
Median Review Time (in days)	183	356
# Drugs reviewed w/in 6 months	36 (49%)	1 (1%)
# Drugs reviewed w/in 1 year	70 (96%)	45 (62%)

The initial PDUFA authorizations were an indisputable success in speeding FDA review times and injecting greater predictability into the way drugs are approved by the agency. However, their initial impact was limited to the period after a new drug application was submitted to the FDA, leaving the much lengthier development process that precedes FDA review unaddressed. But the period in which the FDA reviews a new drug application accounts for only a fraction of the time that it frequently takes to develop a new medicine. Since then, however, the FDA has become increasingly involved at earlier stages of the development process. As such, the FDA has played an increasingly important and active role in reviewing interim results from earlier stage studies, and has provided feedback on research study designs through a variety of meetings with clinical study sponsors. The FDA has also played an increasingly active and valuable role in providing regulatory perspectives and participating in scientific discussions outside of activities related to a specific product application.

Over time, the FDA's more active role in product development has led to expansions to the agreements between the FDA and the drug manufacturers that supply the user fees. Recent user fee agreements have allowed funds to be applied to activities that are beyond the primary application review functions, such as programs to advance the science that serves as the basis for new product development. In addition to funding core product review and personnel, the sixth authorization of the user fee

agreement will support key projects that ensure the FDA can conduct critical scientific programing, participate in public workshops, and develop guidance for its employees and external stakeholders regarding cutting-edge science and new strategies for drug development and regulation.

Highlights of the PDUFA IV Agreement

PDUFA VI Advances the Role of Patients and Their Experiences

As part of the PDUFA V programs, the FDA began to build a robust Patient Focused Drug Development program. This included quarterly public meetings with patients, caregivers, advocates, and FDA personnel. Each meeting focused on a specific disease and was designed to gain insights directly from people who experience that condition on how it impacts their daily lives. The 21st Century Cures Act takes important steps to operationalize this type of feedback. It begins to set up processes to assist organizations and researchers in collecting patient-experience data, creates channels for providing such data to the FDA, and it will help develop methods for analyzing it.⁵ The PDUFA VI agreement further builds on these programs and sets the course for further incorporation of the patient voice in drug development. Under the agreement, user fees will be used to hold public workshops, develop guidance documents, strengthen internal capacity, and establish new methods for clinical outcomes assessments and patient reported outcome measures.

PDUFA VI Supports the Continued Success of the Breakthrough Therapy Designation

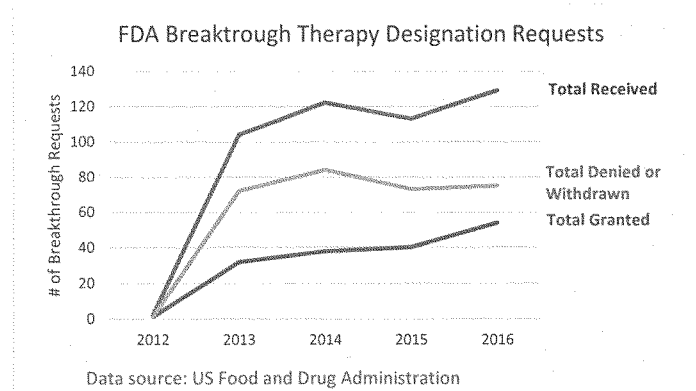
In 2012, the FDA Safety and Innovation Act (FDASIA), which contained the reauthorization of PDUFA V, established the Breakthrough Therapy Designation. This designation may be given to a drug intended to treat a serious illness for which preliminary clinical evidence indicates a substantial improvement over any existing intervention.⁶ This designation was rapidly implemented into drug development programs,

⁵ PL 114-255. The 21st Century Cures Act. Title III Subtitle A Patient Focused Drug Development

⁶ PL 112-144. FDASIA Sec. 902 Breakthrough Therapies.

and to date, 170 Breakthrough Therapy Designations have been granted, leading to 79 indications approved by FDA using this process (Fig 2).

Figure 2. Breakthrough Therapy Designation Use 2012-2016



Year	Total Received	Total Granted	Total Denied	Total Withdrawn
2012	2	1	1	0
2013	104	32	62	10
2014	122	38	70	14
2015	113	40	52	21
2016	129	54	62	13
2017	35	5	8	0
Total	505	170	255	58
Data source: US Food and Drug Administration				

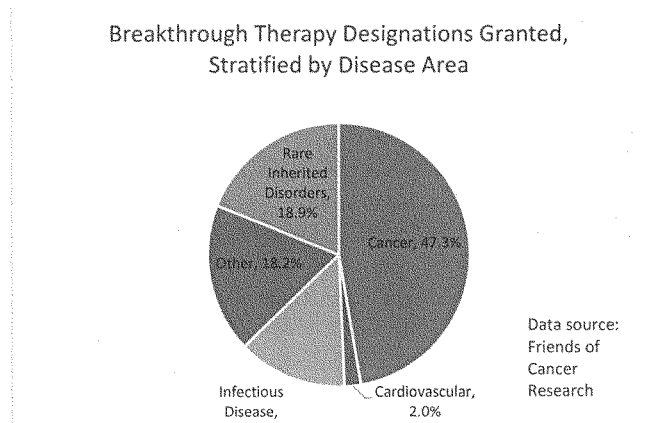
When the Breakthrough Therapy Designation is granted by the FDA, an intense collaboration is initiated between the agency and the sponsor to expedite the development of the drug. This process results in near real-time interactions between the FDA and sponsors, the involvement of senior leadership at the FDA, use of cross disciplinary project teams for optimal coordination of different application components, and consideration of different study designs that can minimize the number of patients

exposed to inferior agents throughout clinical testing. While these process enhancements can add efficiencies to the development process of drugs that demonstrate extraordinary clinical activity, they are also resource intensive. As indicated in Figure 2 by the more than 500 requests for Breakthrough Therapy Designation received since FDASIA established the designation in 2012, it is a widely-used program that continues to demand a heavy workload from the FDA.

In a recent analysis to explore the impact of the designation for new oncology products, we found that breakthrough-designated cancer drugs were reviewed in an average timeframe 3 months shorter than for those without the designation. While review times are important, the key goal of the Breakthrough Therapy Designation is to expedite drug development. It does so by acknowledging that new drugs demonstrating transformative potential early in their clinical testing may be permitted to employ novel approaches to demonstrate the safety and efficacy required for approval. Upon examining the pre-market development time of new cancer drugs, calculated as the number of years from submission of an investigational new drug (IND) application to submission of a new drug application (NDA) or biologics license application (BLA), we found that development time was 2.2 years shorter for approved breakthrough-designated drugs than for those without the designation.⁷ While this may be attributed in part to differences in natural disease trajectory of different cancers, the observed difference in development times provides preliminary evidence for the positive impact of the Breakthrough Therapy Designation and the collaboration it spurs. It is important to note that the Breakthrough Therapy Designation has been applied in a variety of different disease settings (Fig. 3), with under half of publicly disclosed designations going to products that treat forms of cancer.

⁷ Shea M, et al. *Impact of breakthrough therapy designation on cancer drug development*. Nat Rev Drug Dis. Vol. 15 p. 152. March 2016.

Figure 3. Breakthrough Designations by Disease



The PDUFA VI agreement will provide critical resources to allow the successful Breakthrough Therapy Designation to continue to facilitate rapid access to highly promising new medicines for patients suffering from serious diseases.

PDUFA VI Promotes Qualification and Use of Drug Development Tools

Developing new drugs is an incredibly risky process. The probability of an experimental drug compound progressing from Phase 1 trials to FDA approval was recently estimated to be 9.6% for all drug categories and 5.1% in oncology.⁸ A major driver of this low success rate is the uncertainty drug developers face when testing a new drug. It takes time and careful study to identify whether the patients selected for a clinical study are most likely to benefit from an experimental therapy and to

⁸ Clinical Development Success Rates 2006-2015. BIO, Biomedtracker, Amplion: 2016. Accessed at: <https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO.%20Biomedtracker.%20Amplion%202016.pdf> Accessed 3.19.17

determine how they respond to treatment. Questions such as: “Is a patient likely to develop side effects?” and “How far has the disease progressed?” and “Does a potential treatment target the correct disease pathway?” are routinely asked by drug developers and can be addressed efficiently through the use of biomarkers and other drug development tools.⁹ They help researchers answer these questions by providing rapid, reliable information on key metrics including drug safety, pharmacodynamics and drug response.

The FDA has a program to “qualify” certain biomarkers and other drug-development tools, which provides drug developers with the assurance that the methods they use have been scientifically vetted. This has the potential to rapidly speed the pace of drug development and prevent waste created by the case-by-case approach to biomarker qualification that the FDA has adopted in the past.¹⁰ The present PDUFA reauthorization package contains important provisions to enhance the biomarker qualification process. It instructs the FDA to publish two draft guidance documents on standards and taxonomy for biomarker qualification, as well as to convene a public workshop to engage the public on these topics.

By facilitating the development of new markers that can serve as intermediate indicators of safety or efficacy, the clinical testing process is improved. The use of validated biomarkers can help identify patients for which a drug is likely to work, offer early indicators of toxicity that help improve patient safety, and in some cases indicate that a drug will have a longer term benefit and allow for earlier access to promising new drugs. The resources provided in the PDUFA VI agreement will help create a process in which new biomarkers and other drug development tools can be accurately assessed and ensure their appropriate use.

⁹ Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. *Clinical Pharmacology & Therapeutics*. Volume 98 Number 1: July 2015.

¹⁰ Ibid.

PDUFA VI Enhances the Use of Real-World Evidence in Regulatory Decision-Making

Clinical trials are typically conducted in highly controlled populations to maximize the probability of success. However, once a drug reaches real-world populations, there may be unanswered questions about a drug's effect in patients with characteristics not represented in clinical trials. The collection of real-world evidence (RWE) allows for a greater understanding of drugs currently in use. Real-world evidence is gathered by processing data from electronic medical records (EMRs) and tracking patient outcomes over time. This type of evidence has the potential to supplement the knowledge gained from pre-market studies and can aid in regulatory decision-making. Under PDUFA VI, the FDA will engage patients, industry and academia to better understand how RWE can be collected and used to support high-quality evidence generation and regulatory decision-making. By allocating user-fee funding toward these programs, the FDA and other stakeholders will be able to identify limitations and explore different opportunities for the use of data collected from post-market experience with a drug.

For Additional Consideration*Effectively Communicating Scientific Advances*

Rapid advancement in science and technology allows our understanding of new and current drugs continues to grow. In the years following FDA approval, new data about drug safety and efficacy emerges rapidly through post-market clinical studies and real-world experience captured in day-to-day medical practice. While new safety information is readily incorporated into drug labeling, new information about drug efficacy is often not submitted to FDA for labeling updates. Despite its absence on approved labeling, new information is quickly synthesized by clinical guideline developers, which is then used to inform clinical practice. This drives the high rate of off-label prescribing, which has become commonplace; indeed between one half and three quarters of all oncology prescribing is done off

label.¹¹ That off-label use is based on varying levels of supportive evidence. One study found that 27% of off-label uses were backed by strong evidence, with the remaining uses lacking strong scientific support.¹²

After reviewing collections of drug-related information published by clinical-guideline developers, called compendia, we found additional evidence of off-label use. When we compared drug compendia to existing FDA drug labels, we found that compendia recommended additional uses beyond the scope of those described in product labels for 79% of oncology drugs. Of the additional uses recommended by compendia, 91% were recommended by uniform consensus among the physicians developing the guidelines and recognized as acceptable uses by the four largest private insurers.

The variance between FDA labels and drug compendia indicates that there is a significant opportunity to improve how emerging scientific evidence can be incorporated into product labels. Currently, sponsors can submit a supplemental new drug application to modify a product label with additional efficacy claims. However, there may be instances when the efficacy profile of a drug has evolved but no supplemental application to the label was ever submitted. This typically happens when incentives to submit additional information are limited, such as when a drug has gone off patent and faces generic competition, or when a drug is no longer actively marketed.

Because PDUFA VI tasks the FDA and other stakeholders with exploring uses of post-market evidence, we believe that such information needs to be scientifically rigorous to appropriately inform patient and

¹¹ Mullins CD, Montgomery R, Abernethy AP, Hussain A, Pearson SD, Tunis S; American Society of Clinical Oncology. Recommendations for clinical trials of off-label drugs used to treat advanced-stage cancer. *J Clin Oncol*. 2012 Feb 20;30(6):661-6.

¹² Radley D, Finkelstein S, Stafford R. Off-label Prescribing Among Office-Based Physicians. *Arch Intern Med*. 2006 May 8;166(9):1021-6.

practitioner decisions. When post-market data presents compelling evidence for a new use of an approved product, the FDA could play a greater role in evaluating the relevant data to update the product label, as appropriate. This would allow independent experts at FDA to adjudicate between uses backed by strong evidence and those backed by less persuasive evidence, and to establish a standard by which post-market evidence should be evaluated.

Restoring the relevance of FDA-approved labels is an important public health goal. While other high quality sources of clinical prescribing information exist, FDA labels remain the sole source of information carrying the weight of a scientific agency with decades of experience reviewing drug efficacy data. Ensuring that processes are in place to modify outdated product labels can help ensure that use of the product is supported by the highest quality of evidence possible, and that patients and physicians can have confidence in supplemental uses of approved drugs.

Current Challenges to the FDA

Despite opportunities afforded by PDUFA VI, the passage of the 21st Century Cures Act, and the enormous contributions of this committee, I would be remiss to state that the FDA and the people who rely on it are optimally positioned at present. Even so, proposed cuts to biomedical research will put the brakes on the engine of discovery, abandon progress on new tools to enhance product evaluation, impede opportunities for new businesses in the biotech sector, and most perilously, jeopardize the development of new medicines for patients desperate for progress. Holding the FDA budget authority at stagnant levels prevents progress on agency functions that are not applicable to user fees. These include critical functions of the agency such as drug-safety surveillance programs, oversight of drug compounding facilities, review of product advertising material, oversight of over-the-counter medicines,

and conduct of scientific programming. Compounded with the constraints of the federal hiring freeze, the FDA will be hamstrung. The ramifications will be felt for years to come.

Among the challenges that have been exacerbated in the current environment is the implementation of the FDA Oncology Center of Excellence (OCE). The 21st Century Cures Act included a directive for the agency to establish an initiative to coordinate activities within the three current medical product centers around one or more major disease areas.¹³ To begin this work, the FDA established the OCE in recognition that cancer has evolved to require multimodal technologies for optimal management. For example, drugs are being developed with increased frequency to treat cancer using genetic information to guide their use. This can involve review divisions of CDER for the drug product, or CBER in instances of cell-based gene therapy or vaccines, and CDRH for a diagnostic. Housing these functions and expertise within the OCE can enhance collaborative interactions and streamline administrative processes, facilitating rapid and thorough development and application review. Ultimately, this type of coordination will add efficiencies to the development of new technologies, bring a uniform approach to assessing benefits and risks, and allow cutting-edge treatments to reach patients as quickly as possible. But reaching this goal has been stymied by the current environment. The reality of lagging funding, the potential of a detrimental budget future, and the presence of a hiring freeze place this transformational opportunity at significant risk. As Congress resolves the budget for FY18, clarification that funds dedicated to the cancer moonshot can be transferred to the FDA for the OCE would provide important core support.

Despite challenges ahead that may weigh progress down, scientific advancement has brought us to a time of great opportunity. For the people who currently depend on safe and effective medicines, for

¹³ PL 114-255. The 21st Century Cures Act. Title III Subtitle G Sec 3073: Establishment of Food and Drug Administration Intercenter Institutes.

those who are holding strong for the breakthroughs to come, and for every future patient, there isn't time to waste. The work that will be made possible through innovative policy like the 21st Century Cures Act will catalyze progress and improve lives and health of Americans. Building on these advancements, we urge Congress to swiftly pass this sixth reauthorization of PDUFA. In addition, to fully capitalize on this progress, and ensure that patients and physicians have access to the highest quality post-market evidence, new processes should be developed to maintain more up-to-date drug labels. Finally, for the programs of this proposed user fee agreement to succeed, the full budget for the FDA must be robust, and the capacity at which the agency can maintain and hire the best scientific minds must be unencumbered.

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For more information please contact: Ryan Hohman, JD, Vice President, Public Affairs, Friends of Cancer Research at rhohman@focr.org or 202.944.6708

Mr. GUTHRIE. Thank you. Thank you for your testimony, and I now recognize Ms. Holcombe for 5 minutes for your opening statement.

STATEMENT OF KAY HOLCOMBE

Ms. HOLCOMBE. Mr. Vice Chairman, Ranking Member Green, and members of the subcommittee, Bio appreciates the opportunity to speak with you today about the sixth reauthorization of the Prescription Drug User Fee act. Let me begin by stating unequivocally that BIO strongly supports this PDUFA VI user fee agreement and its timely authorization.

Nearly 25 years ago, completing action begun by this committee, Congress passed the first PDUFA after agreeing with FDA and the biopharmaceutical industry that providing additional staff funded by user fees would help FDA review applications more quickly. You were shown to be spectacularly right. Today in this final year of PDUFA V, FDA is the most efficient drug regulatory agency in the world. American patients are the beneficiaries.

The success of PDUFA in bringing down the time of new drug review has led over the years to substantial expansion of the program in terms of the numbers and kinds of commitments FDA has made annually from increasing its efficiency in communicating with drug developers to enhancing its post-market surveillance and monitoring of drugs throughout their life cycles to applying best review practices across all review divisions to enhancing processes to review and approve therapies for rare diseases to executing systematic approaches to measuring the benefit-risk ratio of potential drugs and to seeking and incorporating patient perspectives in that assessment.

What has worked relative to review of applications has also made a difference in drug development. In PDUFA VI that is taken to a new level. FDA formal review time is the mere tip of the iceberg of time patients wait for new drugs. Review timelines are significant not only because they are short, but also because they are predictable and predictability is critical for companies making investment decisions. It would be highly desirable if the same sort of efficiency and predictability were achieved throughout drug development.

PDUFA VI builds on the proven premise that greater and more productive interaction between drug developers and FDA works. It leads to better outcomes and to more efficient development programs. A greater focus on drug development improvements in PDUFA VI is not at the sacrifice of what has been achieved for review times, 8 months for priority applications and 12 months for standard.

The PDUFA VI goals, including expanding expertise in diverse statistical methods, piloting innovative clinical trial designs and computer modeling and simulation, use of biomarkers as surrogate endpoints, and more frequent and appropriate use of real-world evidence or big data will transform drug development. All of these goals which attempt to bring 21st century science to the fore in this agreement will augment, not completely replace, tried and true methods of data collection. In the end, these new approaches will add to the old to make drug development more efficient while not

compromising the statutory gold standard of substantial evidence of safety and effectiveness.

PDUFA VI also will take patient focused drug development to new levels. The message of these commitments is that the patient voice truly matters, in the beginning when early studies show a promising treatment and at the end when FDA is making its decision about a product's benefit and risk. PDUFA VI will bring the patient voice to the forefront, changing it from a voice with a compelling story to a voice that provides evidence, verifiable, valid evidence that is appropriate for the drug label.

Finally, Mr. Chairman, I want to emphasize how crucial it is that FDA has the ability to hire and retain the people it needs to carry out its PDUFA goals and to do that without jeopardizing the other significant parts of its public health mission. PDUFA is a carefully negotiated agreement that takes account of input from all stakeholders including FDA, industry, patient and consumer groups, and others. The key questions on the table are what needs to be changed or enhanced and what is the actual verifiable cost of achieving those goals?

The majority of costs paid by user fees are for personnel. This agreement is carefully crafted to ensure that FDA can bring those people on board who are needed to meet the goals, employees who costs are paid by user fees. In PDUFA VI, the annual hiring goals are included in the agreement. This allows the public a line of sight into whether goals may fall by the wayside as a result of an inability to hire.

Mr. GUTHRIE. Thank you. You need to summarize or is that your conclusion?

Ms. HOLCOMBE. In conclusion, I want to reiterate BIO's strong support for this agreement. It satisfies our basic goals of financial transparency, long-term program viability, hiring and retention improvements to ensure stability and achieve the agreed-upon goals. The vision of PDUFA VI is the vision of 21st Century Cures. Put patient needs—

Mr. GUTHRIE. Thank you.

Ms. HOLCOMBE [continuing]. For access to new medicines first.
[The prepared statement of Kay Holcombe follows:]

**Testimony of Kay Holcombe, Senior Vice President, Science Policy,
Biotechnology Innovation Organization**

**United States House of Representatives
Energy and Commerce Committee, Subcommittee on Health
Hearing on "Examining FDA's Prescription Drug User Fee Program"
March 22, 2017**

Mr. Chairman, Ranking Member Green, and Members of the Subcommittee:

BIO appreciates the opportunity to speak with you today about the reauthorization of the Prescription Drug User Fee Act program (PDUFA). BIO strongly supports this fifth reauthorization of PDUFA and urges timely Congressional action.

I am Kay Holcombe, the Senior Vice President for Science Policy at BIO. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. While our membership includes most of the large biopharmaceutical companies, the vast majority of our members are small biotechnology companies working on cutting-edge R&D. They have small staffs, no marketed products, and no profits, and they are heavily reliant on private capital to fund their work. They take enormous risks every day to develop the next generation of biomedical breakthroughs for the millions of patients suffering from diseases for which there are no effective cures or treatments today. BIO is proud of their innovative spirit and their dedication to alleviating human suffering.

All FDA stakeholders – the biopharmaceutical industry, patient and consumer advocates, health care providers, payers, and others in the healthcare system – recognize the importance of the PDUFA program. Many of them recall the time before enactment of PDUFA I in 1992, when FDA review times were lengthy and a high percentage of new drugs were on the market outside the United States before American patients had access to them. It was first at this Committee that FDA testified that review times could be reduced significantly if the agency could hire the additional staff, funded by user fees, needed to carry out the activities related to review of human drug applications more quickly.

PDUFA I proved this proposition. By the end of the five years of that first PDUFA program, review times had dropped by as much as three-fold. This significant improvement in review times has continued throughout the 24 years of PDUFA. Today, thanks to the resources PDUFA has provided FDA, U.S. patients are – in the vast majority of cases – the first in the world to have access to approved new drugs.

Formal FDA review time is, in fact, the shortest part of the process of moving a new therapy from its inception as a scientifically well-founded hypothesis to its use by patients. Today, it takes 10 to 12 to even 15 years and upwards of \$2 billion to move a drug or biological product from a good idea to an approved product. During that lengthy period, unmet medical needs remain unmet and patients wait. Over the course of four previous PDUFA reauthorizations, the question has been raised as to whether and how the sorts of efficiencies that reduced review times also could reduce drug development times. How can FDA use PDUFA resources to address lengthy, expensive, risky drug development times?

PDUFA V, the program currently in place, was the first to include regulatory science initiatives – development of expertise in FDA to deal with cutting-edge technology and new ways of thinking about the studies and data associated with working toward approval of a new drug. PDUFA V provided funding for modest programs related to patient-focused drug development, the use of pharmacogenomics data, biomarkers as surrogate endpoints, patient-reported outcomes, and meta-analysis – some areas where additional expertise and resources could advance the science and the success rate. A key rationale for inclusion of those initiatives was that they are emerging areas in drug development that hold potential for reducing development times. Addressing drug development times would be a recurring theme entering this PDUFA reauthorization cycle.

Overall Goals for PDUFA VI

As BIO approached this reauthorization of PDUFA, we asked our member companies what they hoped to gain. We heard two themes: advance ways to reduce the time of drug development and ensure that PDUFA remains viable into the future. As to the former, our principal goals were to integrate the patient perspective in drug development; incorporate the use of innovative clinical trial designs, biomarkers as surrogate endpoints, and real-world evidence into acceptable approaches to drug development; and enhance some existing FDA processes, including the review of combination products that will be at the heart of personalized medicine. As to the viability of the PDUFA program, we sought to increase the transparency and accountability of PDUFA financial management and assure the long-term financial stability of the PDUFA program, including through a new time reporting system that would allow accurate capacity planning. Finally, but of primary importance, we sought to work with FDA to improve the agency's ability to attract, hire, and retain the numbers and kinds of employees it needs to do its job as efficiently and effectively as possible.

Program Sustainability and Financial Transparency

Since PDUFA finances and personnel form the foundation that keeps the PDUFA program viable, it is important to look at the situation as it exists today and what needs to be addressed. Since 2002, the PDUFA program has grown at an average of 11% per year; this is unsustainable moving into the future. Changes are needed that address the fee collection structure to increase efficiency and reduce administrative burdens for both FDA and companies. These include reducing the volatility of fee collections, eliminating complicated collection and other financial mechanisms that are difficult to administer, improving predictability, and reducing variation of collections year over year. Together,

these changes will increase efficiency and reduce program growth rate substantially. Specifically, the PDUFA VI proposals would:

- limit the carryover balance levels, thus reducing possible over-collection of fees and the need for complicated administrative mechanisms to deal with such over-collections;
- eliminate supplement fees, which will further simplify fee collections;
- replace the current Product and Manufacturing fees with a new Program fee that will constitute 80% of the annual fee collections; and
- reduce the percentage that Application fees contribute to the total from the current 33% to 20%, thus mitigating the overall impact of this difficult-to-predict revenue source.

Increased financial transparency will provide a greater line of sight by Congress and the public into how PDUFA fees are collected and allocated and a more accurate picture of the costs associated with human drug review activities. This will be accomplished under PDUFA VI by improving resource management, thus allowing the public to know accurately how PDUFA fees are being used and to understand clearly the costs associated with human drug review related activities, and by providing a publicly available 5-year financial plan and annual updates of how the agency is executing against that plan. In both the development of the initial plan and throughout the remaining years of PDUFA VI, public input will be sought through public meetings and other mechanisms.

Transparency also will be increased as regards the calculation of the PDUFA workload. Until PDUFA VI, PDUFA fees have been adjusted annually by applying an inflation factor, which is straightforward and understandable, and a workload adjustor, which is neither. More than one outside consultant has stated that, while there is a clear need to apply an adjustment factor to account for differing workloads year over year, the particular adjustment factor was not a good one but was the only possibility unless there was systemic change in the way workload was measured. That systemic change is coming in PDUFA VI.

Beginning now, and through PDUFA VI, FDA will implement a new time reporting system, in which time and costs are measured on a continuous basis, rather than by sampling at pre-determined time periods throughout the year. This kind of system, used by multiple private sector organizations as well as in many government programs, provides significantly more accurate data than are now available on which to base workload calculations. FDA will be advised and assisted in establishing and executing the new system by an outside contractor with expertise in such systems. Progress toward this implementation and initiation of the new adjustment factor will be publicly available information, reported in the PDUFA annual Performance Report.

These more accurate time and cost data also will contribute to the ability to plan for future resource needs, contributing to the long-term sustainability of the PDUFA program. A capacity planning function will be established, which will allow FDA to assess in advance the number of staff that will be needed to assure a continuing efficient and effective human drug review program. Achievement of this goal is

under way, with a third-party expert already working with the agency on determining the best approach to development and use of capacity planning.

Personnel Management

Hiring and retaining the expert staff essential to carrying out user-fee-funded activities is critical for PDUFA VI to work. Without the necessary number and kinds of staff, FDA simply cannot meet the performance goals for which user fees are intended. Problems with FDA recruitment and hiring have existed for years, for a number of reasons, including cumbersome hiring processes and pay scales that generally are lower than for similar positions in the private sector. The 21st Century Cures Act, from this Committee, addressed some of the issues that have hindered FDA's ability to attract, hire, and bring on board the kinds of senior scientific and medical staff needed. Those provisions will make a significant positive impact. In addition, under PDUFA VI FDA has committed to make changes in its internal personnel operations, including implementing a dedicated senior scientist recruiting function, increasing staff capacity to recruit and to process personnel actions in a timely way, and engaging the services of independent contractors to assist in these functions, advise the agency in best human resources practices, and evaluate and report annually and publicly on hiring and retention progress.

For the first time, hiring goals are included in detail in the PDUFA VI Performance Goals Letter, and achievement of these goals will be detailed in the annual PDUFA Performance Reports. Many of these changes already are under way. For example, FDA has begun the process of hiring staff to replenish the long-under-staffed Office of New Drugs, responsible for the review of all new drug and biologics applications. This hiring in FY 2017 is funded from PDUFA V amounts in the carryover balance. The balance exists as a result of earlier sequestration and continuing resolutions, which prevented the allocation of some PDUFA V resources before now. This hiring will continue in the first several years of PDUFA VI, along with hiring of additional staff essential to carry out the new performance goals agreed to between FDA and industry, in collaboration with other stakeholders such as patient, consumer, and provider organizations.

Over the course of PDUFA VI, the negotiated and agreed-upon number of FTEs (full-time equivalents) necessary to carry out the goals of PDUFA VI is 230, hired over years of the user fee agreement, FY 2018 to 2022. These include medical reviewers, pharmacologists, pharmacists, chemists and other scientific experts, biostatisticians, financial managers, and other essential staff. In each year's performance report, beginning in FY 2018, FDA will report on its progress in achieving the hiring goals specified in the PDUFA VI Goals Letter.

To summarize our views on the financial and hiring enhancements of PDUFA VI: BIO believes they are on target and essential to ensure both the long-term viability of this crucially important use fee program and to ensure that FDA is able to hire, bring on board, and retain the expert staff who are crucial for the agency to meet its PDUFA VI goals and, in general, to carry out its public health mission. We all have the same goals – ensuring that FDA-approved safe and effective therapies are available to patients as soon as possible. This Committee addressed them in 21st Century Cures; we add to that work through the PDUFA VI goals.

Making a Difference for Drug Development = Making a Difference for Patients

PDUFA VI promises to transform drug development. We believe FDA can and will deliver on this promise, provided they continue to have the ability to hire the additional people needed to carry out the historic commitments of this agreement.

In the beginning, the intention of prescription drug user fees was to improve the efficiency of FDA's review and reduce its time. That goal has been achieved. Today, the vast majority of new drugs are available to U.S. patients before they are available to patients anywhere else. FDA is the fastest and most efficient drug regulator in the world. All those who supported the establishment of the PDUFA program have been proven right. In August 1992, then-FDA Commissioner David Kessler made his first appeal to Congress in his testimony before this Committee, that if the agency had access to greater resources through a user fee program, review times could be reduced significantly. Industry, though with some skepticism, agreed. The Committee reported the first user fee bill shortly thereafter, with strong bipartisan support, and PDUFA was signed into law on October 19, 1992, by President George H.W. Bush. The rest is history.

Over the course of the four reauthorizations of PDUFA and as a result of user fees, we have seen review times drop dramatically from what they were before 1992, and we have seen other changes as well, such as enhancement in FDA's efficient and effective communication with applicants; augmentation of the agency's ability to monitor and assure the safety of products both pre- and post-market, throughout product life cycles, including establishment and use of the Sentinel program; adoption of best practices for scientific review and communication across all the review divisions in the Centers for Drugs and Biologics; establishment and implementation of regulatory science programs to deal more effectively with emerging areas of product research and development, such as the use of biomarkers, pharmacogenomic data, and patient-reported outcomes; and multiple other goals to ensure timely, efficient review. While all of these goals were being achieved, review timelines were not negatively affected. FDA consistently has met or exceeded its established goals of completing the review of Priority applications in eight months (many such priority applications are completed in fewer than eight months) and of Standard applications in 12 months. These timelines are now the global gold standard for regulatory efficiency. In the U.S. our economy has benefited from PDUFA, because drug and biologic applicants now have greater certainty of a reasonable timeline for completion of their applications. Most importantly, though, patients have benefited. Before PDUFA, U.S. patients legitimately could say that their counterparts elsewhere in the world had treatments available before they did. That largely is not the case anymore.

For nearly its entire history, PDUFA has been focused principally on the timeliness and efficiency of the formal FDA review process after an application has been submitted for approval. Yet FDA's application review time of less than 12 months pales by comparison to the 10 to 12 years on average that it takes to develop a drug – time before an application even is submitted to the FDA. Development of new medicines is a long and rigorous process, and it has become more costly and complex over the past decade – partly because the science is harder, and partly because the regulatory review process has not kept up with the advancing science.

The question facing PDUFA VI stakeholders and FDA was the question that faced this Committee as it embarked on 21st Century Cures: What can be done to change the course of drug development and to reduce the time it takes to get to that goal of submitting an application to FDA?

To tackle these questions, it was important to identify what new tools are available today that aid in drug development. Advances in biology have made miracles such as gene therapy more than a pipe dream or science fiction. Are there other advances that, if used to greater advantage, can accomplish the miraculous with respect to drug development?

The authors of 21st Century Cures and the PDUFA VI agreement independently recognized some of the same new tools and developed proposals and PDUFA VI commitments that would allow these tools to be used most effectively, with the goal of ensuring more timely availability of new drugs for patients by reducing the time and increasing the chance of success of drug development.

Key Drug Development Goals of PDUFA VI

Integrating the Patient Voice in Drug Development and Regulatory Decision-Making

One of the most important goals of PDUFA VI was building on the success of the PDUFA V Voice of the Patient program, in which public meetings brought FDA and patient representatives together so the agency and other stakeholders could hear how these patients perceived their condition, what they hoped for in terms of a “benefit” from a therapy, and how they viewed “risk.” Those meetings, and the reports produced from them, were a positive step forward in terms of bringing these patient perceptions into the FDA determination of the benefit-risk calculus. Patients augmented that deliberation by adding the crucial patient perception dimension to an often largely mathematical and statistical evaluation. They also helped drug developers to understand better what patients viewed as their needs, so this could be taken into account when planning and executing a development program.

The next step in this approach is to engage patients and other stakeholders in another public process that will result in guidance, developed by FDA with stakeholder input, in a step-wise fashion. First, guidance will be developed regarding how to collect evidence-based and representative patient information. Next will be guidance on processes and approaches to determine what is most important to patients in terms of the impacts of their disease and potential impact of new treatments. This will be followed by guidance on how to measure impacts in a way that will facilitate meaningful patient input into the design of clinical trials. This is particularly important in light of the cost and length of clinical trials, the difficulty of enrolling sufficient numbers of patients, and the risk of patient drop-out, which can compromise or even negate the trial results. Finally, FDA will re-visit its existing guidance on patient-reported outcomes and address incorporating clinical outcome assessments into endpoints.

To accomplish these objectives, FDA will strengthen its staff capacity, including bringing on board experts in psychometrics and health outcomes research. These staff will be integrated into the review teams to ensure the engagement of patients and to consult with drug developers during their development programs.

Ultimately, the goal of good data collection, representative sampling, and appropriate use of data is to be able to include information on the drug label that can be used by prescribers, patients, and caregivers. The drug label is the trusted source of information about the best and safest ways to use a drug. Reliable patient input into belongs in that label, and this PDUFA VI agreement will help make that happen.

Enhancing Benefit-Risk Assessment

FDA established a structured benefit-risk approach under PDUFA V. In PDUFA VI, implementation of this approach will be enhanced through one or more public meetings with and for stakeholders, and through development and publication of guidance on the use of the benefit-risk framework throughout the drug life cycle. The incorporation of patient perspectives will be a key part of these activities. An independent third party will evaluate the implementation of the benefit-risk framework and whether it is being implemented consistently across the review divisions. The importance of this goal is three-fold: first, it solidifies and evaluates the use of the benefit-risk framework, which allows greater transparency for all stakeholders into FDA's thinking about how to measure the potential benefits of a potential new drug against its known risks; second, it emphasizes the importance of patient input into this crucial decision; and, third, it helps drug developers use the benefit-risk assessment as a marker and a tool in the course of the development of a drug and throughout its lifecycle.

Enhancing Communication between FDA and Drug Sponsors

PDUFA VI builds on the enhanced communications program established under PDUFA V, which was intended to assure that sponsors were able to receive timely responses to inquiries that could be dealt with outside of the formal FDA-sponsor meeting process. Under PDUFA VI, a third party will evaluate how this program is proceeding, how such informal communications are handled across review divisions, and what best practices may be adopted across the board. A public meeting will allow stakeholders an opportunity for discussion and input into the evaluator's findings.

Using Drug Development Tools, including Biomarkers

In PDUFA VI, FDA is committed to enhancing biomarker qualification processes. In addition, the agency will implement a pilot program to seek and incorporate the input of external experts to assist in the qualification, to verify if the use of such outside experts can make the processes more timely and efficient. In addition, the agency will augment its staff capacity to conduct qualification of drug development tools, hold a public workshop particularly aimed at discussing nomenclature, standards, and elements of a biomarker qualification plan; publish guidance; and publish and update lists of qualified biomarkers and of pending applications. Significantly, FDA will establish a process for holding dedicated meetings with sponsors to discuss the use of biomarkers as surrogate endpoints. This will be a new meeting, additional to those meetings that all drug developers are entitled to have with FDA during their development programs.

Using Real-World Evidence

The Sentinel system, established by FDA in response to Congressional direction, is the source of enormous data regarding the health care and health outcomes of tens of millions of patients covered by several private insurance plans. FDA uses the system to search for safety signals that may lead to further investigations regarding the safety of marketed drug products. The system is supported by a number of sources, including user fees. Under PDUFA VI, prescription drug user fees will provide \$50 million to continue to support the operation and use of Sentinel. FDA will work, during the course of PDUFA VI, to ensure that stakeholders, including industry, are well informed about how the agency is using the system and to seek additional ways to help others, beyond FDA, access this treasure trove of data while protecting any patient and drug sponsor confidential information.

In addition to the data available through Sentinel, there are multiple other sources of “real-world evidence” that currently are seen primarily as a potential source of drug safety information. Under PDUFA VI, FDA will hold a public meeting and, based on that input, develop pilot studies or related activities to determine other uses of such real-world data in regulatory decision-making. One possibility is that large data bases could be used as a source of information that could augment other sponsor-developed data in applications for approval of a new indication for an already approved drug. Another possible use is for the fulfillment of post-marketing requirements associated with newly marketed drugs.

Data are everywhere. The question PDUFA VI will begin to answer is how such data can be harnessed and used effectively to advance, enhance, and reduce the time of drug development.

Improving the Review of Combination Products

Combination products – which join two drugs, a drug and a biologic, or a drug or biologic and a medical device, commonly a diagnostic test – pose some unique challenges to developers. Streamlining and better assignment of roles and responsibilities at FDA could help address these challenges and advance these products, which many see as a wave of the future. For example, personalized medicine is highly dependent on identifying, often through a diagnostic test, patients who will benefit from a particular drug and those who are likely not to benefit, or who may be subject to greater risk. Such advancements will not only benefit patients, but also facilitate the broader move toward a more cost-effective healthcare system.

The challenges that have been identified as slowing the review of such products include the decision as to which FDA Center has primary or lead responsibility, which Center has decision-making authority, and how to speed the work of the “other” Center that may not have a user fee goal impetus to make a particular application a priority. PDUFA VI will address these challenges in several ways. First, staff capacity and training will be increased in all three medical product Centers, the Centers for Drugs, Biologics, and Devices. PDUFA funds will be used for bringing staff on board in all three Centers. Second, performance goals will be established specific to combination products and will be phased in over the course of the 5 years of PDUFA VI. Submission procedures and guidance related to unique features of combination products will be developed and published.

Using Innovative Clinical Trial Designs

Clinical trials are the most costly and difficult parts of drug development, and their design, enrollment, and execution can add extraordinarily to the time of drug development. Many experts in trial design have argued that the “traditional” randomized, double-blind, controlled trial is not always the most efficient or necessary approach. With new ways of thinking, and given new approaches to statistical analysis, are there better ways to do trials without losing their validity, their amenability to appropriate data analysis, and, thus, their contribution to the most appropriate regulatory decision?

In PDUFA VI, FDA is committed to beginning to answer that question. First, additional FDA staff, particularly additional biostatisticians, and especially those with training and expertise in “non-traditional” statistical analysis, will be added. FDA will hold a public workshop on innovative trial design and will publish guidance on adaptive trials. Finally, and of particular significance for moving this idea forward, FDA will conduct a pilot program focused on innovative trial designs. This program will be voluntary – i.e., companies may opt in to the program and, in exchange for their participation, will be given two meetings with FDA to discuss the proposed trial design and its execution, to enhance the likelihood of success of the development program. Companies in the program will agree to allow FDA to discuss the trial design as a case study at a subsequent public workshop or in guidance (protecting all company-specific confidential information). Participation in the pilot program is voluntary, but the hope is that there will be strong participation, so the ability for others to learn from case studies will “raise all boats,” expand the use of innovative trials, and contribute to reducing the time and cost of clinical trials.

Using Model-Informed Drug Development (MIDD)

Biological and statistical modeling can contribute greatly to a knowledge base that can advance drug development, reduce the time of development, and allow development to proceed even in cases where clinical data may be limited. FDA will explore the use of MIDD through both increasing its staff capabilities and establishing a voluntary pilot program similar to that for innovative clinical trial design. In addition, the agency will hold workshops to identify best practices for various types of modeling and publish guidance based on its findings through the workshops and in the pilot program. Modeling informs development, and is not intended as a complete substitute for clinical data. Part of the importance of this program is that it can determine how modeling can assist in moving forward a significant development program where clinical data are limited. Modeling or simulation would not be the only source of data in any program of developing a human drug.

Continuing and Enhancing Successful Programs

PDUFA VI will continue and enhance its efforts related to the highly successful Breakthrough Therapy program, which has shown the power of enhanced communication between FDA and sponsors to speed drug development for exciting new products; augment its capacity and enhance its processes for reviewing applications for rare disease therapies, to continue its record of success in prioritizing these applications based on the high unmet medical need of patients with rare diseases; and continue and build on the successful New Molecular Entity (NME) review program, which has accomplished its goal of

increasing the number of products approved after only one cycle of review. All of these programs are resulting in reducing the time of drug development. All of them are verified and verifiable successes.

PDUFA VI and 21st Century Cures: Great Minds Think Alike

When this Committee embarked in a bipartisan effort to learn how to advance science and regulation in ways that would lead to better, healthier lives for patients, it identified – through consultation with experts around the country, including patients, caregivers, regulators and former regulators, industry, and many others – it achieved the near-impossible. It found suggestions common to many disparate stakeholders for improving the processes of basic research that are fundamental to understanding disease and treating it and for improving the processes of translating that research into real products that are safe and effective and can be made available to patients. In the latter category were suggestions that focused on improving drug development timelines through applying new tools and new ideas and encouraging and directing FDA to incorporate those into its thinking when reviewing applications.

Perhaps not surprisingly, some of these tools and ideas also came into the discussions between FDA and stakeholders in developing the PDUFA VI agreement. The skeptical might worry that such an overlap of ideas in two separate and very different contexts is a recipe for disaster. Not so. In fact, there is the best sort of overlap between the provisions of 21st Century Cures and PDUFA VI – the kind that results in each enhancing the other. A few examples, not an exhaustive list, are illustrative.

Biomarkers – a word that has, over the last two years, come into the lexicon of people who never thought of a biomarker before – are a focus both of PDUFA VI and of 21st Century Cures. The Act and PDUFA VI are complementary, in terms of ensuring that FDA has and uses effectively an efficient process for qualifying biomarkers; publishes guidance to help applicants for biomarker qualification understand the taxonomy and data standards; makes public a list of qualified biomarkers and pending applications; and engages external experts in biomarker qualification.

Patient-focused drug development – in this area as well, it is clear that there is near-universal agreement on the need to do more, and in a more systematic way, to incorporate the patient perspective into drug development and regulatory decision-making. Guidance development, public meetings, development of methods and standards for collecting information and data, and use of patient perception and experience information in the FDA regulatory decision about the benefits and risks of a drug are all elements of both 21st Century Cures and the PDUFA VI agreement.

Real-World Evidence – there is considerable overlap between the provisions of 21st Century Cures and PDUFA VI. 21st Century Cures provides helpful context for the work under PDUFA VI, and provisions of the two that differ are easily harmonized.

Innovative Trial Design – while 21st Century Cures focuses on adaptive trials and Bayesian approaches, PDUFA VI takes a broader approach, opening its pilot program to other trial designs while also highlighting adaptive trials and Bayesian approaches. Public processes, including workshops, and guidance development are parts of both.

In short, it surely is the case, looking at PDUFA VI and 21st Century Cures together, that there is broad agreement about what is needed to reduce the time of drug development.

BIO strongly supported and applauds the enactment of 21st Century Cures, as we strongly support the PDUFA VI negotiated agreement. We believe that, together, these two efforts will make a difference for patients.

BIO urges Congress to act swiftly to move the PDUFA VI reauthorization forward. This agreement, negotiated between FDA and the biopharmaceutical industry with input and support from multiple other stakeholders, positively advances our shared goal of making safe and effective treatments available to patients as efficiently and quickly as possible.

Thank you for the opportunity to present our views today. I am happy to answer any questions you may have.

Mr. GUTHRIE. Thank you very much. Now Dr. Pritchett, you are recognized for 5 minutes for opening statement.

STATEMENT OF ANNE PRITCHETT

Ms. PRITCHETT. Good morning, Vice Chairman Guthrie, Ranking Member Green, and members of the subcommittee. I am please to appear before you to provide PhRMA's perspective on the timely reauthorization of PDUFA. PhRMA, as you know, represents the country's leading innovative biopharmaceutical research companies which are devoted to developing new medicines that enable patients to live longer, healthier, and more productive lives. We appreciate the opportunity to testify and share our views on PDUFA VI.

For over 2 decades, PDUFA has helped to bring innovative medicines to patients by providing greater clarity and predictability in the science-based drug review process. Today, I just want to briefly share PhRMA's perspective on the PDUFA program and key elements of the PDUFA VI agreement.

First, I just want to note that we view user fees as an important mechanism to support the critical work of the FDA and human drug review process, and note as a result of this program over 1,500 new drugs and biologics have been approved since 1992. The number of new medicines being approved on their first review cycle is at a historic high, and as we heard earlier, the review times have dramatically dropped by more than half since the 1990s as a result of this agreement.

As a result of PDUFA, the U.S. leads the world in the introduction of new medicines and is a global leader in biopharmaceutical R&D. I would note at a time when other countries are seeking to attract and grow their own biopharmaceutical presence due to its far-reaching economic impacts, it is more critical than ever that we ensure that the U.S. retains its competitive advantages which includes a science-based gold standard regulatory system in the FDA, one that facilitates the ability of our industry to harness the latest scientific and technological advances and to translate those into new treatments and cures for patients.

I would note that PDUFA VI is a result of extensive negotiations between the FDA and the innovative biopharmaceutical industry and it really includes unprecedented input across all stakeholders. Patients and patient advocates in particular played an important role by providing input on potential PDUFA VI goals through formal stakeholder meetings with the agency as well as frequent interactions with industry, and that feedback is reflected in several of the provisions. I would note failure to reauthorize PDUFA in a timely manner would obviously negatively impact the FDA's ability to carry out its important role in fostering the introduction of new medicines to patients.

And I want to briefly touch on some key elements of the agreement. First, obviously PDUFA VI facilitates science-based integration of the patient perspective into the development and regulatory review of innovative medicines. Over the course of PDUFA VI, FDA will be holding a number of workshops to gather stakeholder input to inform a range of guidances that are focused on how do we bet-

ter incorporate the patient element into all stages of drug development and review.

Second, PDUFA VI enhances the FDA's access to the tools, processes, and expertise necessary to ensure that the FDA is ready for the 21st century, the latest scientific advances in drug development and regulation. Specifically, as mentioned by other witnesses, there will be an increase in the FDA's capacity to qualify biomarkers. The agreement advances the use of real-world evidence building on 21st Century Cures facilitates the appropriate use of innovative clinical trial approaches.

Third, PDUFA VI will accelerate the development and availability of new medicines to patients while providing the scientific and regulatory predictability that will foster a continued biopharmaceutical innovation. PDUFA VI not only builds upon the highly successful new molecular entity review program, which has led to shorter review times and an increase in first cycle reviews, but it builds upon it by incorporating additional metrics.

Fourth, PDUFA ensures that the FDA will be able to hire and maintain a strong scientific medical and regulatory workforce to advance its public health mission. For the first time, PDUFA VI includes detailed hiring goals and includes dedicated resources for the recruitment and retention of a world-class scientific workforce. And I would note it also includes independent outside consultants to help facilitate the agency in developing a comprehensive hiring strategy.

And finally, the agreement builds on key provisions of the 21st Century Cures Act by further advancing real-world evidence, incorporating that into a structured benefit-risk framework, patient-focused drug development, biomarker qualification, as well as includes a number of improvements to combination product review.

I want to conclude by saying PhRMA and its member companies we are committed to working closely with the FDA, your committee, Congress, and all stakeholders to ensure the continued success of PDUFA in bringing safe and effective innovative medicines forward to address unmet medical needs for all patients. We believe that moving all of the UFA's forward in a timely manner is important to supporting the FDA's mission of protecting public health and promoting innovation, as well as critical to supporting our shared goals of fostering continued competition and innovation. Thank you for the opportunity to testify today.

[The prepared statement of Anne Pritchett follows:]

Testimony of

**Anne Pritchett, PhD, Vice President, Policy and Research,
Pharmaceutical Research and Manufacturers of America (PhRMA)**

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

Hearing on “Examining FDA’s Prescription Drug User Fee Program”

March 22, 2017

Good afternoon Chairman Burgess, Ranking Member Green, and the Members of the Subcommittee:

My name is Anne Pritchett, Vice President, Policy and Research, at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to developing medicines that enable patients to live longer, healthier and more productive lives. Since 2000, PhRMA member companies have invested more than half a trillion dollars in the search for new treatments and cures, including \$59.6 billion in 2015 alone.

I am pleased to appear before you to provide PhRMA's perspective on the importance of the Prescription Drug User Fee Act (PDUFA) and its timely reauthorization. As you know PhRMA served as industry's principal negotiators with FDA for the PDUFA VI agreement. Our members are committed to the research and development of new therapies that enable patients today to live longer, healthier and more productive lives and through a robust pipeline of more than 7,000 investigational medicines, providing patients with hope for the treatments and cures of tomorrow.

Today, I will briefly speak to PhRMA's perspective on the successes of the PDUFA program and key elements of the PDUFA VI agreement.

Perspectives on the Success of the PDUFA Program

In the midst of the HIV/AIDS crisis of the 1980s, the United States lagged behind other countries in the review and approval of new medicines. The FDA faced a significant backlog in the regulatory review of new drug applications and was unable to keep pace with the workload related to the human drug review program. An average FDA review time of approximately 29 months meant that in many instances new medicines were approved in other countries, months or years before they were available in the United States. This unacceptable delay compelled the patient advocacy community to catalyze a nationwide demand for faster review of drug applications. As a result, the first PDUFA was passed in 1992, giving the FDA the additional resources needed – through the collection of user fees – to improve application review times.

For nearly twenty-five years, PDUFA has provided much needed resources to the FDA's human drug review program that has resulted in greater certainty and predictability for patients who depend on safe and effective innovative medicines. PDUFA VI builds upon the successes of previous PDUFA agreements with continued focus on ensuring patient safety, maintaining the FDA's high standards for regulatory review, and, ultimately, promoting timely access to safe and effective innovative medicines, including treatments for patients with rare, serious, or life-threatening diseases.

The PDUFA program has produced positive and tangible results that matter to patients, ensuring that FDA's review process for new medicines keeps pace with biopharmaceutical innovation:

- **FDA has approved over 1,500 new drugs and biologics** since 1992, including treatments for cancer, cardiovascular, neurological, infectious and rare diseases.ⁱⁱ

- **The number of new medicines being approved on their first review cycle is at a historic high**, including approvals for new medicines to treat rare diseases.ⁱⁱⁱ
- **Review times for drug applications have dropped by nearly 55%.** The median approval time for standard applications has decreased from 22.1 months in 1993 to an estimated 10 months in 2015.^{iv} The median approval time for priority applications has similarly decreased from 13.2 months in 1993 to an estimated 7.9 months in 2014.^v

As a result of PDUFA, the “drug lag” between the United States and the rest of the world has been eliminated, and the United States leads the world in the introduction of new medicines without compromising FDA’s appropriately high safety or efficacy standards. At a time when the economic competitiveness of our nation is recognized to be strongly rooted in our capacity to advance innovation-based industries, PDUFA VI is critical to providing the capabilities and efficiencies needed to encourage the significant R&D investments made by biopharmaceutical companies in the U.S.

Key Elements of PDUFA VI

The PDUFA VI agreement will help ensure the long-term stability of the user fee program, provide necessary resources and enhancements to FDA’s human drug review program, and strengthen the scientific capabilities of the agency. Specifically, PDUFA VI will:

- Create efficiencies that can accelerate the development and availability of new medicines to patients, while providing greater predictability that will continue to foster biopharmaceutical innovation.
- Enhance the FDA’s access to the tools, processes, and expertise necessary to keep pace with the latest scientific advances in drug development and regulation.
- Facilitate the systematic integration of the patient perspective into the development and regulatory review of innovative medicines.
- Ensure that FDA can hire and retain a strong scientific and medical workforce to advance its public health mission.

The PDUFA VI agreement strengthens pre-market review and post-market safety, enhances FDA’s regulatory decision tools, and promotes financial accountability and capacity planning. We have identified some of the important provisions outlined in the agreement that will help to speed drug development, streamline the review process, and provide more options to innovative medicines for patients.

Improvements to Pre-Market Review and Post-Market Safety

As a focal point of PDUFA V, the New Molecular Entity (NME) Review Program has been very successful, as review times have been reduced, first cycle approvals have increased and the predictability for sponsors and patients has been strengthened through enhanced communication during the review period. PDUFA VI not only continues the NME Review Program, but will also build upon it by incorporating additional metrics to enhance the drug

review and approval process. As part of the review, FDA will provide a timeline for drug scheduling recommendations during the pre-submission meeting and updates on these activities during the Mid- and Late-cycle Review meetings. In addition, FDA will update the Good Review Management Principles and Practices (GRMPs) guidance to include review activities not currently associated with specific PDUFA goals.

Under the PDUFA program, FDA and industry have worked together to ensure that meetings during the drug development phase are as efficient, substantive, and timely as possible. PDUFA VI will provide additional time for FDA's review of meeting materials for Type B and Type C meetings, while also providing sponsors with responses to their questions 5 days in advance for scheduled meetings. These changes will lead to more substantive engagements between FDA and sponsors and reduce the need for multiple meetings. This will allow for drug development programs to proceed in a timelier manner and expedite availability to new medicines for patients.

As a cornerstone of the PDUFA V agreement, the breakthrough therapy program has been a profound success. The response to the program has been remarkable—a sign of the swift pace of new scientific advances—and substantially more resource intensive for FDA to manage than anticipated. No additional resources were provided for this function in PDUFA V. PDUFA VI will dedicate significant new resources to the program to ensure that the workload is manageable and patients continue to gain expedited access to treatments for serious and life-threatening diseases that are currently without adequate treatment options.

The PDUFA program dedicates substantial resources to help ensure the safety of medicines when they are on the market. PDUFA VI will expand these efforts by providing significant resources to enhance the FDA's ability to review, track, and communicate important post-market safety information to patients, physicians, industry, and key stakeholders.

Enhancing FDA's Regulatory Decision-making Tools

Patients and patient advocates played an important role in the PDUFA VI reauthorization process by providing input on potential PDUFA VI goals through formal stakeholder meetings with the agency and frequent interactions with industry. Patient group feedback is reflected throughout the PDUFA VI agreement. In particular, two provisions bring the patient voice directly into the development and review process:

- PDUFA VI will strengthen the FDA's capacity and capability to advance the science of patient input in the drug development and regulatory review process, including the use of patient-reported outcomes measures.
- Over the course of PDUFA VI, FDA will conduct a series of public workshops to gather stakeholder input to inform several guidances related to patient-focused drug development, the use of patient-reported outcomes, and the structured assessment of the benefits and risks of new medicines. Facilitating the development and application of scientific methods that incorporate the patient perspective into drug development will help ensure that medicines better reflect measures that are meaningful to patients.

PDUFA VI will also help facilitate the appropriate use of innovative clinical trials designs, including convening a workshop, publishing draft guidance, and conducting a voluntary pilot

program. Innovative clinical trial approaches have the potential to enhance the efficiency of the drug development and regulatory review process, and help accelerate patient access to safe and effective new medicines.

“Model-informed drug development” and related statistical and modeling approaches have the potential to accelerate the development and availability of innovative medicines. PDUFA VI will establish processes to allow for the use of model-informed drug development to help reduce drug development and review times to make the interpretation of data more efficient while protecting patient safety.

PDUFA VI will increase staff capacity and resources for the qualification of biomarkers, including piloting approaches to engaging external experts in FDA’s qualification process. As biomarker science has been progressing faster than regulatory acceptance, it is important that we shorten the time between biomarker discovery and assimilation into practice. A number of aspects of PDUFA VI seek to address this:

- FDA will hold a public workshop on biomarker qualification and publish guidance documents to provide all stakeholders, including academia, patient groups and biopharmaceutical companies, with further clarity on the data necessary to qualify a biomarker.
- A dedicated process will be created for scientific consultation between the Agency and sponsors for drug development programs that plan to use a biomarker as a novel surrogate endpoint.

Real-world evidence provides a valuable source of information about the safety and effectiveness of a medicine in a broader population beyond that studied in clinical trials. Advancing the science of using real-world evidence in regulatory decision-making, including studies based on electronic medical records and patient registries may accelerate the clinical development of additional uses for a medicine as well as the assessment of the benefits and risks of medicines. PDUFA VI will advance the potential use of real-world evidence for regulatory decision-making through public workshops with key stakeholders, pilot studies with sponsors, and the publication of guidance on how real-world evidence can contribute to the assessment of the safety and effectiveness of medicines.

Promoting Financial Accountability and Capacity Planning

The PDUFA VI agreement supports common sense financial reforms that provide greater predictability for the Agency. These reforms include reducing FDA’s administrative burden and operating expenses for the PDUFA program without compromising the human drug review program performance, regulatory review standards, or patient safety. PDUFA VI reallocates the fee collection structure of the program, eliminating the establishment fee and providing more revenue through approved products, which enhances predictability, improves strategic planning, and provides better management of Agency resources.

PDUFA VI modernizes FDA’s human resource capacity and capabilities to provide more accountability to stakeholders, including patients. FDA will implement a full time reporting system and establish a professional capacity planning function to better track workload, identify

areas of need, and help reallocate resources when necessary. PDUFA VI will also provide resources for an independent contractor to assess the program and help to implement best practices to ensure the program remains adequately and appropriately funded for the future. Determining the most appropriate fee levels and ensuring the resources are most efficiently being utilized will provide FDA with the tools to further improve their capabilities as well as continue to ensure access for new products.

In order for FDA to have the ability to perform its duties of delivering safe and effective new medicines to patients and ensure the continued regulation of products throughout their lifecycle, it is imperative the Agency has the appropriate staff and expertise available to them. The human drug review program at FDA has been understaffed and has lacked certain scientific capabilities needed to fully achieve its goals. PDUFA VI will address this issue through providing dedicated resources for recruiting and retaining a world-class scientific and medical workforce, providing independent outside consultants to work with the Agency on a comprehensive hiring strategy, and for the first time including hiring goals within the agreement. These provisions will help ensure FDA is delivering new medicines to patients in a timely manner, and that they are prepared for the increasingly complex drug development and review challenges of the 21st Century.

Conclusion

At a time when the U.S medical innovation ecosystem is facing severe strains and increased global competition, it is imperative that the FDA is equipped to help us deliver the next generation of new treatments and cures to meet patients' unmet medical needs. PDUFA VI will help the FDA ensure that patients receive effective and lifesaving drugs, while maintaining the United States' global leadership in biomedical innovation.

PhRMA and its member companies are committed to working closely with FDA, and all stakeholders, to insure the continued success of PDUFA in bringing safe, effective innovative medicines forward to address unmet medical needs for all patients. PhRMA therefore urges Congress to reauthorize PDUFA in a timely manner to ensure the new enhancements are implemented as quickly as possible and protect against any disruptions to this important program.

PhRMA applauds your continued commitment to ensuring the long-term sustainability of the FDA's human drug review program and to continuing to strengthen the agency's capabilities in areas critical to keeping pace with the latest scientific advances in drug development and regulation. We look forward to continuing to work with the Subcommittee, members of Congress, and other stakeholders on these important issues. Thank you for the opportunity to provide this testimony.

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- i | U.S. Food and Drug Administration (FDA), FY1995 Performance Report to the President and Congress for the Prescription Drug User Fee Act.
www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm117257.htm.
- ii | U.S. Food and Drug Administration (FDA), PDUFA Background and Reauthorization Process (Presentation by Theresa Mullin). 15 July 2015 <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM455134.pdf>
- iii | John Jenkins, FDA. CDER New Drug Review: 2015 Update (Presentation). 14 December 2015
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM477020.pdf>
- iv | FDA, FY2015 Performance Report to the President and Congress for the Prescription Drug User Fee Act,
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM497750.pdf>
- v | FDA, FY2015 Performance Report to the President and Congress for the Prescription Drug User Fee Act,
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM497750.pdf>

Mr. GUTHRIE. Thank you all for your testimony, and we will now move into the question and answer portion for our second panel. And I will begin the questioning and recognize myself for 5 minutes.

First, I would like to request unanimous consent for entering the following statements in the record: the Rare Disease Legislative Advocates, the RDLA blog, PDUFA RDLA, Congress Begins Process of Reauthorizing Prescription Drug User Fee Act; a letter from the Epilepsy Foundation, letter; number three, National Venture Capital Association blog post on PDUFA; and four pieces I am asking to enter into the record, National Organization for Rare Diseases and Friends of Cancer Research joint statement on PDUFA.

Mr. GREEN. No objection.

Mr. GUTHRIE. No objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. GUTHRIE. So Mr. Allen, actually Mr. Sarbanes was talking about this earlier with Dr. Woodcock, and where I kind of wanted to look at about labeling. And after a drug is approved, more and more information is often learned about it. This can include new uses, more tolerable doses, et cetera. And for cancer drugs, can you talk about the disparity between the information in products labeling and how the drug is actually being prescribed and administered by oncologists?

Mr. ALLEN. Sure. So typically a manufacturer would, if they are pursuing an additional indication for a drug, would take it and submit it through the supplemental new drug application at the FDA for that information to be evaluated. But in some instances like I mentioned, when a drug is off patent or perhaps even for a particularly rare population where a clinical trial is difficult or infeasible, or in some cases because the drug has been on the market for so long may be unethical, the label oftentimes doesn't reflect the practice and the use of that drug over time.

And what we found by comparing the FDA labels to practice guidelines that are constructed by medical oncologists is that the uses that are recommended by expert oncologists are usually far beyond that of what is contained in the FDA label. So the question is, should the product label have a role in the agency which we trust to evaluate medicines for them to get on the market, should they have a more active role in looking at potential label modifications further down the life cycle of the drug to ensure it is supported by the highest quality evidence.

Mr. GUTHRIE. Do you think FDA needs to clarify when and how companies can provide such information?

Mr. ALLEN. In terms of when it can be supplied to them?

Mr. GUTHRIE. Yes.

Mr. ALLEN. I think it could—

Mr. GUTHRIE. When it needs to be.

Mr. ALLEN. The agency certainly does in terms of safety, but the same mechanisms aren't in place with regards to alternative uses. So one could imagine that perhaps it is worth having a longer discussion about the ability for over a certain period of time perhaps after the patent expires that there be some process for review of post-market evidence in order to make sure that the way the drug is being used is supported by the highest quality of evidence, so the

people who are prescribing and using it are able to tell the difference between what is high quality and what is just an anecdotal use.

Mr. GUTHRIE. OK. And I had another question, but I think you did answer it that do you believe FDA should play a more active role in updating product labeling, and you answered that actually when you answered the first question.

Mr. ALLEN. Yes. I think it is worth a longer conversation because obviously there are resource implications. But given the oncology anyway there are highly qualified professional guidelines that might help the FDA conduct post-market analyses when it is appropriate to review a growing body of evidence.

Mr. GUTHRIE. Right. Yes, that is something that we just need to work to make sure we can clarify that because I think Dr. Woodcock was sharing similar to that when she was talking to Mr. Sarbanes about, some oncologists has a different tumor that this actually has effect for and works for and would be logical to use, but we need to make sure that it can be done through the process.

So thanks for your testimony, and actually I will yield back my extra minute and I will yield to Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman.

Ms. Holcombe, current statute outlines a detailed process for reauthorization of the PDUFA. The FDA is charged not only with negotiating with the industry to develop recommendations, but also to solicit public input and hold public hearings and consult periodically with Congress and patients and consumer groups, among others. The recommendations that are a result of this process must also be available publicly for the public comment and ultimately required by statute to be transmitted to Congress by January 15th of this year. The process that led to the ultimate transmission of FDA PDUFA VI recommendations kicked off nearly 2 years ago in July of '15.

Ms. Holcombe, can you further discuss industry's role in the reauthorization of PDUFA and particularly the timeline for these activities?

Ms. HOLCOMBE. So as you point out, Mr. Green, this process began in July of 2015 with a public meeting at which all stakeholders were provided an opportunity to testify, and industry took advantage of that opportunity and presented our views about the importance of PDUFA in general and about some specific enhancements to the program that we would be seeking in our negotiations with FDA. Those negotiations kicked off approximately 2 months later and lasted then for over 12 additional months and were intensively focused on the calculation of what could be done and how much it would cost to do each one of those things.

And both FDA and industry put ideas on the table, and those ideas were frequently, if not every single time, informed by the input of other meetings that were going on simultaneously with patients in the other groups that you mentioned, so it was a very long process and I would say mathematically and statistically a very precise process.

Mr. GREEN. Well, since this is our sixth time on it, hopefully we learn something every time.

Ms. HOLCOMBE. Well, we are getting faster.

Mr. GREEN. OK. The statute requires that a recommendation be transmitted to Congress no later than July 15th of '17, a deadline they met. Does the statute allow the FDA to transmit recommendations for reauthorization at an alternative date?

Ms. HOLCOMBE. Not that I am aware of.

Mr. GREEN. OK. PDUFA expires on September 30th of '17. What would be the impact for your member companies if Congress did not pass the reauthorization of PDUFA before the September 30th deadline?

Ms. HOLCOMBE. I think we would describe the implications as titanic in nature. FDA would be required, if this were not reauthorized, to reduce its force by probably in the Drug Center alone about 5,000-plus individuals, and those are the people who review our applications. But even more importantly than the review of applications, which as we have all said today is merely the tip of the iceberg of our process of drug development, it would absolutely disable any process that FDA has for talking to us during drug development about how to be more successful in our program.

Mr. GREEN. Do you support and your industry support PDUFA VI recommendations as transmitted to Congress?

Ms. HOLCOMBE. Yes, we do.

Mr. GREEN. OK. You note in your testimony that the drug development process, the most time-intensive part of bringing a drug to market, it is my understanding that on average it takes between 10 to 12 years to develop a drug. Recognizing this, we included in the 21st Century Cures a revision that would have FDA host a public workshop and issue guidance on innovative trials and designs and approaches.

Would you please explain further how innovative trial designs may help your member companies in bringing treatments to market quicker and, in addition, would you discuss how PDUFA VI builds off of the Cures' effort to support the use of innovative drug trial designs?

Ms. HOLCOMBE. Yes. So as my testimony pointed out great minds think alike, and we in the industry as well as FDA itself agreed a hundred percent with you in your identification in 21st Century Cures of the importance of thinking of different ways to do clinical trials than the traditional way of randomized controlled trials.

Often clinical trials have to enroll many, many people and they take a long time. And as Dr. Woodcock pointed out, they often have high dropout rates. Patients can't stay in them, and these cause drugs to fail and at great expense to companies that are developing them. So innovative ways of thinking, creative ways of thinking could we do trials differently and therefore make them shorter and smaller but still come out with the substantial evidence of safety and effectiveness that we all need to have and the answer to that is yes, we can.

Mr. GREEN. OK. Mr. Chairman, I know my time has expired. And Mr. Allen, I would like to submit some more questions to you, but obviously FDA is working with you on the off-label usage that practitioners learn, and we need to be able to learn what they are learning so we can actually make those pharmaceuticals available and go back through the FDA process as brief as we could do to make sure those cures are there. So thank you, Mr. Chairman.

Mr. GUTHRIE. Thank you. Thank you. The gentleman's time has expired. Dr. Bucshon, you are recognized for 5 minutes for questions.

Mr. BUCSHON. Thank you, Mr. Chairman. First of all, I mean, I also want to go on the record saying I have concerns about the budget proposal as it relates to research, the NIH and above. I don't think that is a partisan issue.

The question I have is as we transition to new models to approve medicines we have been talking about that whether that is changes in clinical trials or other things, how do you see the legal environment evolving to allow this to happen? I will start with Dr. Pritchett. Because, I mean all of us are realists. I was a medical doctor before, as you transition to a new way to approve a product there is going to be people out there that are looking to throw a wrench into the gears by saying it didn't prove what it was supposed to prove and that is why my particular client has been hurt. And so I mean there are legal ramifications of trying to do this also, any thoughts?

Ms. PRITCHETT. So I think as I understand your question, as we think about looking at innovative, new approaches to clinical trials, collection of real-world evidence and how do we apply this to drug development and then how do we ensure that we are using them in a robust way so that we are reducing any potential concerns related to liability, ensuring that we aren't approving medications without appropriate evidence—

Mr. BUCSHON. Essentially that is the question, because that is one of the things that drives up costs of drug approvals. Everybody has to look at those issues, but a percentage of the drug costs are because of these type of issues. My question would be basically is, I mean, yes, what are our thoughts about that? Do we need, I mean obviously we are working on tort reform in other areas. Any thoughts on that process as it relates to the drug product development?

Ms. PRITCHETT. So I am not prepared to discuss that today. We would be happy to come back and have further discussions with you. I would note that as we look at the PDUFA process, part of the engagement by FDA in providing very clear guidances to industry is to help avert any potential concerns from a liability perspective, et cetera, but I think this is an important topic that we would welcome to have further discussion.

Mr. BUCSHON. OK, because I could see that the FDA and others very quickly retract their thoughts on these things as soon as we have some big class action lawsuit against the FDA and everybody else.

Ms. PRITCHETT. I think that is a very important issue that you are raising and we would greatly appreciate coming back and having further discussion on that topic. I appreciate you raising it.

Mr. BUCSHON. OK, great, any other comments from the other panelists?

Ms. HOLCOMBE. I think one of the important things to recognize about PDUFA VI is that in some respects takes account of this type of concern by initiating under PDUFA VI pilot programs, where the agency and the industry are going to work together to pilot these various trial designs or model-informed drug development ap-

proaches and determine whether in fact with input from outside stakeholders, whether these kinds of designs, this kind of way of developing drugs is going to produce the sort of good evidence, solid evidence that we need to make sure this product is safe and effective when it goes on the market.

Mr. BUCSHON. OK, anything else? Well, anyone, for all of you, can anyone give us a sense of how they envision the FDA utilizing the authorities in 21st Century Cures Act in PDUFA VI, that the provisions involving the use of real-world, so-called real-world evidence to support their decision making how we would envision that being incorporated?

Ms. HOLCOMBE. Well, I think as Dr. Woodcock said, FDA already uses real-world evidence in the determination, making determinations about potential safety signals of marketed drugs. So the question is in PDUFA VI, is it possible to use real-world evidence, i.e., patient experience with drugs in the marketplace from medical records or from your Apple watch? Is it possible to harness those data, to validate those data, and to use those data to understand more about how the drug is working, and would those data be helpful then in making a decision about perhaps broadening an indication for a drug that is very narrowly indicated or adding an indication, which goes to the point that Dr. Allen was making about how the drug label can become out of date when medical practice is ahead of what was known at the time the drug was produced.

Mr. BUCSHON. OK. I will just make a quick comment. That is why other issues we are working on like interoperability of electronic medical records is going to be really key to this type of thing. I think everyone would agree to that and I yield back.

Mr. GUTHRIE. The gentleman yields back. Seeing no questions from this side, Ms. Brooks from Indiana is recognized for 5 minutes for purpose of asking questions.

Mrs. BROOKS. Thank you, Mr. Chairman.

Dr. Pritchett, PDUFA VI creates a significantly revised fee structure which replaces current levies on manufacturing facilities and on products. Can you explain this revised fee structure and how is it beneficial for all parties?

Ms. PRITCHETT. I would actually yield to Kay who was directly involved in the negotiations and I wasn't, who I think would be better.

Mrs. BROOKS. I wondered about that after one of her previous answers, but I was suggested to you. So Ms. Holcombe, would you like to share with us?

Ms. HOLCOMBE. The reason for looking at a different way of collecting fees was to try to make sure that we had a system that was administratively as simple as it could be so that it was not so costly or so burdensome on either the FDA and companies. So the way fees used to be collected was they were divided one third among manufacturing facility fees, product fees, and application fees. There were two things wrong with that, at least two.

One thing was that it placed equal emphasis in terms of percentage of dollars collected on all three components, including the application fee which is the least predictable source of revenue. There is very little perfect ability to predict the number of applications that are going to come into FDA on an annual basis. They have a

lot of experience so they can give you a range, but if you collect 50 instead of 60 that makes a huge difference in the total revenue that you are collecting. So could we reduce the dependence on the application fee and increase the dependence on other fees?

The second thing that was wrong was the manufacturing facility fee, which is a nightmare to calculate mostly because drugs aren't just manufactured like I make mine in my facility and you make yours in your facility. Lots of people make drugs in the same facility, so figuring out whose was where when and how often and so forth. So could we offload that fee, could we calculate the rest of the fee based on number of products?

And so we calculated what would that mean if we did certain percentages of collection from that new fee and certain percentage from the application fee? And we developed, or FDA actually developed, not I personally, a tool that companies could use and they could plug into this tool how much money they had paid in fees in previous years and how much they would pay under some new sort of split of the fees.

Mrs. BROOKS. What is the tool referred to by the FDA?

Ms. HOLCOMBE. We called it a widget, OK.

Mrs. BROOKS. OK.

Ms. HOLCOMBE. Yes, my terminology, sorry. It was a tool that allowed you to manipulate the percentage based on, so the total fee collection, let's say, is \$800 million. If you collected ten percent from applications and 90 percent from products, what would that mean for each company? How much would they pay?

So they would plug in their own numbers, like how many applications did they think they would be submitting next year and how many products do they have on the market? And they figured out, bingo, up came this number; this is how much you pay. Well, then they could change that from 10/90 to 20/80. How much would you pay based on your number of products on the market and the number of applications you anticipate submitting, how much would you pay?

And using that tool, we figured out collectively with all of our companies that the ratio that had the least negative impact on the most companies was a 20 percent application fee, 80 percent program fee collection. And although a small number of companies on a percentage basis, out of all the long list of companies that pay fees, did see that their fees would go up slightly, the vast majority of companies saw that their fees actually would go down.

How could that even be, right, but it was. I mean, math, it is just a wonderful science.

Mrs. BROOKS. And if those fees go down what happens?

Ms. HOLCOMBE. The total amount of money collected is still the same because it is spread out across all fee payers.

Mrs. BROOKS. OK, thank you. I am sorry my time is up, but thank you for explaining it.

Ms. HOLCOMBE. I am sorry I don't know the math involved in it.

Mrs. BROOKS. I yield back. OK, thank you.

Mr. GUTHRIE. Thank you, and the gentlelady yields back. Mr. Bilirakis is recognized for 5 minutes for questions.

Mr. BILIRAKIS. Thank you. Thank you, Mr. Chairman. I appreciate it very much.

Ms. Holcombe, back in the 2000s it was recognized that there was a lack of good information on the safety and efficacy of drugs for the pediatric population. Can you talk about some of the incentives that came about to encourage more pediatric clinical studies?

Ms. HOLCOMBE. So the Best Pharmaceuticals for Children Act combined with the Pediatric Research Equity Act have been a very successful way to get more drugs studied in pediatric populations so that information can go on the drug label and pediatricians know how to dose the drugs for children. The incentive that has caused that to be so successful was the addition to whatever regulatory exclusivity the company might have on its product for adults of 6 months for doing these pediatric studies.

And we believe at BIO that incentives such as this one can be very effective in increasing the number of products that are developed in areas for which there is high unmet medical need but very difficult populations or areas of interest, such as, for example, intractable antibacterial resistant conditions. These are tough and there is just no good way of doing it. So incentives can be very effective and they have been for pediatric studies.

Mr. BILIRAKIS. What about the rare disease space? Again there are about 500 approved rare disease drugs, but 7,000 rare diseases affecting approximately 30 million Americans. They are taking medication off-label, and I know the stories because I hear from my constituents on a regular basis. They take the drugs off-label not knowing if their drugs are safe and effective for their conditions or if it is proper dosage—that is so important—and fighting with their insurance companies on coverage of these medications.

Does it make sense to incentivize development for a targeted population when there are clearly defined needs?

Ms. HOLCOMBE. Yes.

Mr. BILIRAKIS. Thank you. Last month my colleague and I, G.K. Butterfield, introduced the OPEN Act for the second time. Much like the BPCA, it creates an incentive to run more clinical trials in the rare disease space where 95 percent of diseases have no FDA approval treatments. This would bring more approved drugs to these patients.

The OPEN Act has the potential to result in hundreds of new drugs and treatments for individuals with rare diseases. Only 150 rare disease patient groups, over 150 at last count, I think it is more than that support this bill. The OPEN Act was part of the House 21st Century Cures Act, and while it fell out at the 11th hour, unfortunately, I am going to continue to push for this legislation. It is a priority for me. Do you have any comments on that? And of course I welcome cosponsors for this legislation as well.

Ms. HOLCOMBE. So it is clear that without the Orphan Drug Act we would not have 500 treatments for rare diseases. It is also a tragedy that we don't have 7,500. And again we believe incentives can work. We don't have an official position on your proposal, but definitely it merits more evaluation.

Mr. BILIRAKIS. All right. Well, thank you very much. I yield back, Mr. Chairman.

Mr. GUTHRIE. Thank you. The gentleman yields back, and seeing no other members wishing to ask questions I would like to thank all of our witnesses for being here today.

And pursuant to committee rules I remind members that they have 10 business days to submit additional questions for the record, and I ask the witnesses submit their response within 10 business days upon receipt of those questions.

Without objection, the subcommittee is adjourned.

[Whereupon, at 12:18 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Thank you, Mr. Chairman. I appreciate the opportunity today to discuss the reauthorization of the Prescription Drug User Fee Act. PDUFA has been incredibly successful at bringing reviews of new drug applications down by more than half, and providing patient access to treatments more quickly, and often before any other country.

PDUFA has also encouraged innovation by bringing stability and predictability to the review of new drug applications. FDA has been able to hire the review staff and scientific and technical experts needed to keep pace with science and increase the efficiency of the review process. However, more work needs to be done and I am encouraged by how PDUFA VI builds off of the successes of this user fee program.

I am therefore disappointed to see what can only be referred to as a disclaimer in the testimony today from FDA. While it is true that the reauthorization proposals were negotiated under a previous Administration, the goals of the PDUFA program and the drug approval process remain the same—a fully resourced and staffed FDA, and an efficient and timely drug review process that is keeping pace with the scientific and regulatory advancements in this field. It is my hope that the Administration would understand how carefully crafted the current agreement is, and recognize that the reauthorization process started nearly two years ago.

The agreement before us today is the result of many negotiations with industry and stakeholders, consultations with patients and consumers, and solicitation of public input. The resulting recommendations were transmitted to Congress in meeting the January 15, 2017 statutory deadline. Transmitting new recommendations at this point would go against this requirement, and run the very real risk of PDUFA not being reauthorized before the program expires on September 30, endangering the review of innovative new drug treatments and threatening the jobs of thousands of FDA employees.

I intend to continue to work with my colleagues on the Committee and across the Capitol, as well as industry, to ensure that we do not let this happen. This is a strong agreement, and one that deserves our support.

Thank you.

Rare Disease Legislative Advocates

Congress Begins Process of Reauthorizing Prescription Drug User Fee Act

March 16, 2017

Timely reauthorization of the Prescription Drug User Fee Act (PDUFA) was one of the hot issues discussed during the Legislative Conference during Rare Disease Week on Capitol Hill.

First enacted in 1992, PDUFA enables the Food and Drug Administration (FDA) to collect user fees from biopharmaceutical companies in order to enable the Agency to review the safety and efficacy of new medicines more quickly. According to PhRMA, it took FDA more than two years to review new medicines and more than 70% of medicines were approved outside of the U.S. before PDUFA.

Every five years, FDA and the biopharmaceutical industry negotiate a new user fee agreement, which Congress must enact in legislation. PDUFA was reauthorized in 2012 in the Food and Drug Administration Safety and Innovation Act, which also included provisions creating the Breakthrough Therapy designation as well as the Rare Pediatric Disease Priority Voucher program. PDUFA is due to be reauthorized this year, as the current user fee agreement expires on September 30th.

Released last year, the draft PDUFA VI agreement includes specific performance goals for drug review, proposed plans for enhanced use of biomarkers, expanded patient engagement, and improved specialization of reviewers for rare diseases.

The Senate Health, Education, Labor and Pensions Committee will convene a hearing on PDUFA reauthorization on March 21st at 10am ET with testimony from senior FDA leadership, and will be available by livestream. The House Energy and Commerce Subcommittee on Health will hold a hearing on PDUFA on March 22nd at 10:15am.

As discussed on the March webinar, it is important for PDUFA to be reauthorized by the end of July or FDA will need to send furlough notices to staff who review new medicines.

<http://rareadvocates.org/congress-begins-process-of-reauthorizing-prescription-drug-user-fee-act/>



March 21, 2017

The Honorable Michael Burgess, Chairman
U.S. House of Representatives
Energy and Commerce Committee, Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Gene Green, Ranking Member
U.S. House of Representatives
Energy and Commerce Committee, Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Burgess & Ranking Member Green:

The Epilepsy Foundation strongly supports the reauthorization of the Food and Drug Administration's (FDA) user fee programs and commends the Energy and Commerce Subcommittee on Health for moving the PDUFA agreement forward in the subcommittee. The Epilepsy Foundation is committed to accelerating the development and approval of new therapies, especially to benefit those in our community with difficult to control seizures and those who experience significant side effects from existing therapies. We support a strong FDA that is responsive to the needs of the patient community and the innovations of scientific research and health care delivery. We urge Congress to move judiciously through the process of reauthorizing the user fee programs and to honor the negotiations that led to the agreements.

The Epilepsy Foundation is the leading national voluntary health organization that speaks on behalf of more than 3 million Americans with epilepsy and seizures. We foster the wellbeing of children and adults affected by seizures through research programs, educational activities, advocacy, and direct services. Epilepsy is a medical condition that produces seizures affecting a variety of mental and physical functions.

The ability of the FDA to properly evaluate and approve therapies so they can enter the market in a timely manner is critically important to the Epilepsy Foundation because of our interest in and need for medical innovation. While many significant advances have been made in epilepsy over the past several years, including the development of innovative medications, medical devices, and surgical options, unfortunately, the number of people with epilepsy who are still experiencing seizures, despite being treated for the condition, has not changed. Today, 1 in 26 Americans will develop epilepsy in their lifetime; however, there is no cure, and even with many drugs and treatment options, one third of people with epilepsy live with uncontrollable seizures. Uncontrolled seizures can lead to disability, injury, and even death. Innovation is of importance to the people with epilepsy for whom available treatments do not work, as well as all Americans living with complex chronic and rare conditions that are not appropriately managed with current treatment options.

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epilepsy.com

The Epilepsy Foundation is your unwavering ally on your journey with epilepsy and seizures. The Foundation is a community-based, family-led organization dedicated to improving the lives of all people impacted by seizures.

These user fee agreements are the result of many years of discussion with all relevant stakeholders, including the FDA, industry, and the patient community. The policies and goals included in the agreements reflect what these stakeholders value and will help ensure advancements and improvements within the FDA and ultimately health care more broadly.

The Epilepsy Foundation applauds congressional and agency leadership for this agreement that will continue the trajectory of patient-centered innovation at the FDA. If you have any questions or concerns, please contact Angela Ostrom, Chief Legal Officer & Vice President Public Policy at aostrom@efa.org or 301-918-3766.

Sincerely,

A handwritten signature in black ink, appearing to read "Philip M. Gattone". The signature is fluid and cursive, with the first name "Philip" and last name "Gattone" being more prominent than the middle initial "M".

Philip M. Gattone
President & CEO
Epilepsy Foundation

Timely Reauthorization of PDUFA & MDUFA Is Critical to VC-backed Life Science Breakthroughs



March 20th, 2017 by [Charlotte Savercool](#) & filed under [Medical Innovation](#), [NVCA Blog](#).

Thirty years ago, the median time for the Food and Drug Administration (FDA) approval of a new drug was 33 months. As one can imagine, major backlog at the agency caused significant delay to the approval and entry of potentially life-saving drugs in the market. To address this problem, Congress passed the Prescription Drug User Fee Act in 1992 to authorize the FDA to collect fees when new drug applications were submitted. Those user fees, paid for by the biopharmaceutical industry, supplemented Congressional funding for the agency to review new drug applications in a more timely and efficient manner. Ten years later, Congress passed the Medical Device User Fee and Modernization Act (MDUFA) after the FDA's medical device program experienced a substantial loss in resources, seeking to accomplish a shared goal (between industry and the FDA) of improving the review process for new medical devices.

Collectively referred to as the "UFAs", PDUFA and MDUFA must be reauthorized by Congress every five years. The reauthorization cycle prompts an important collaboration between the FDA and both biopharmaceutical and medical device industries on a number of items, including evaluation of FDA performance, establishing new goals and objectives, and the negotiation of user fees paid for by industry. Congress then receives the proposed user fee agreement from FDA to convene discussion hearings and ultimately to consider reauthorization legislation.

Life science investors are familiar with the FDA approval process for drugs and devices, and understand the need for a capable regulatory body to accelerate the medical innovation occurring within the industry. Venture investment has driven significant growth into many of our country's most innovative and lifesaving medical products. In fact, the number of life science deals accounted for 12.5% of the overall venture deal count in 2016, investing in some of the most transformative and promising advancements in health care. Last year, \$7.79 billion of venture capital was invested in the pharmaceutical and biotechnology sector and \$3.86 billion of venture capital was invested in healthcare devices and supplies, representing 17% of overall venture activity. Noteworthy examples of venture-backed life science companies include Moderna, a developer of drugs for genetic disorders, hemophilic and blood factors, and oncology; Human Longevity, a developer of genomics and cell therapy-based diagnostic and therapeutic

technology; and CVRx, a developer of implantable technology for the treatment of high blood pressure and heart failure.

It is certainly true that many venture-backed life science startups have seen extraordinary success, but it is important to recognize that medical breakthroughs are extremely challenging and expensive to develop. Those breakthroughs are made even more challenging when there is a lack of certainty on whether FDA will properly staffed and funded. Providing stable funding and resources to meet performance standards at the FDA is absolutely essential for attracting future investment and further expanding our nation's vibrant medical innovation ecosystem.

Over the next several weeks, Members of the Senate HELP Committee and the House Energy and Commerce Committee will hold hearings to examine these user fee programs, starting first with PDUFA and moving to MDUFA later in the month. The UFAs are set to expire the end of September and we are encouraged that Congress is taking significant action toward reauthorization. At the same time, a packed legislative agenda means that Congress and the Trump Administration will need to prioritize reauthorization of the UFAs to meet the September 30 deadline. We encourage policymakers to work in a collaborative manner to ensure medical innovation continues unimpeded.

<http://nvca.org/blog/timely-reauthorization-pdufa-mdufa-critical-vc-backed-life-science-breakthroughs/>

NORD and Friends of Cancer Research Issue Joint Statement In Advance of This Week's Congressional Hearings on FDA User Fees

March 21, 2017

Washington, D.C., March 21, 2017—The National Organization for Rare Disorders (NORD) and Friends of Cancer Research, two leading organizations that collectively represent millions of Americans with cancer and rare diseases, issued the following statement in advance of this week's congressional hearings on the reauthorization of FDA user fees:

"We wish to congratulate the Senate Committee on Health, Education, Labor, and Pensions (HELP) and the House Committee on Energy and Commerce (E&C) for moving forward with the reauthorization of the FDA user fees. This week's hearings represent important steps forward in the renewal of these critical programs.

We also wish to convey our support for the Commitment letters already negotiated and finalized by FDA and regulated industries. The PDUFA Commitment Goals Letter includes several important improvements and advancements to FDA processes and initiatives. These include the continuance of the Patient-Focused Drug Development program, the strengthening of the Breakthrough expedited review pathway, and the expansion of the Rare Diseases program, among others.

The MDUFA Commitment Goals letter also contains several crucial reforms including

the further inclusion of patient preference information and patient-reported outcomes in device development and review, as well as the creation of the National Evaluation System for health Technology (NEST).

Our request of the Committees of Jurisdiction and Congress as a whole is simple: please keep the user fee reauthorization process non-partisan, uncontentious, and focused on the patients FDA serves every day.

The FDA largely relies on user fees authorized by Congress to operate. Without the user fees, a majority of drug, biologic, and device reviewers would be laid off, and the necessary review of innovative therapies would be substantially impaired if not halted all together.

The user fee acts are far too important to jeopardize with controversial partisan policy topics. We recognize the desire for additional reforms related to therapeutic development incentives, review, and access. But we respectfully request that attempts to reform these areas without full bi-partisan support are not pursued as part of the UFA reauthorizations.

The cancer and rare disease patient communities rely on FDA to ensure that innovative, safe, and effective treatments reach those in need. We thank the HELP and E&C Committees for moving forward with these critical funding mechanisms, and look forward to their swift and unimpeded passage."

<https://www.focr.org/news/nord-and-friends-cancer-research-issue-joint-statement-advance-week%E2%80%99s-congressional-hearings>