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

## HEARING

OF THE

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

## UNITED STATES SENATE

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING FDA USER FEE AGREEMENTS, FOCUSING ON IMPROVING MEDICAL PRODUCT REGULATIONS AND INNOVATION FOR PATIENTS

APRIL 4, 2017

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# C O N T E N T S

## STATEMENTS

## TUESDAY, APRIL 4, 2017

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

**TUESDAY, APRIL 4, 2017**

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

The committee met, pursuant to notice, at 10:02 a.m., in room SD–430, Dirksen Senate Office Building, Hon. Lamar Alexander, chairman of the committee, presiding.

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

## OPENING STATEMENT OF SENATOR ALEXANDER

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

This morning, we are holding a hearing on FDA User Fee Agreements: Improving Medical Product Regulation and Innovation For Patients, Part II. This is a bipartisan hearing. Senator Murray and I called the hearing together and invited the witnesses together. We'll each have an opening statement, Senator Murray and I, and then we'll introduce our panel of witnesses. After our witness testimony, Senators will each have 5 minutes of questions.

This is our second hearing on reauthorization of the Food and Drug Administration medical device and drug user fees. FDA is the agency responsible for making sure that patients benefit from the promising research driven by the 21st Century Cures Act, which this committee worked on last year in a bipartisan way, and which Majority Leader Senator McConnell called the most important piece of legislation last year.

Two weeks ago, this committee heard from experts at the FDA who told us that a timely reauthorization of these user fee agreements is integral to helping patients and continuing implementation of the 21st Century Cures Act. I asked the witnesses at the last hearing what will happen if we do not reauthorize by the end of July, 20 days before the authority to collect user fees expires, and here is what they said. Dr. Janet Woodcock, head of FDA's drug center, agreed that cancer drugs would be delayed and said that patients developing resistance to existing cancer drugs might soon not have innovative ones approved soon enough to help them.

Dr. Jeffrey Shuren, the head of the device center, said,

> "We'd lose about a third of our people, and it's not just that reviews will take longer, but the industry, which now is starting to bring their innovative technologies to the United States early, sometimes first, as you heard with the artificial pancreas, they're going elsewhere."

Dr. Marks, head of the biologics center, talked about how ongoing research would be slowed if FDA did not have the staff to provide feedback to companies and scientists. Dr. Marks said,

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

That is what the experts from FDA told us 2 weeks ago, and it is why I am committed to working with Ranking Member Murray and members of this committee to reauthorize these four different user fee agreements before the August recess. The user fee agreements and commitment letters, part of the agreements between FDA and industry that establish the agency's commitments in exchange for the fees Congress authorizes, have gone through an extensive process.

In Congress, while we were working on the 21st Century Cures Act and after it was signed into law, the HELP Committee had 15 bipartisan briefings, some of which were with the Energy and Commerce Committees and the House of Representatives as well, to hear from the FDA and industry about the reauthorization. The first of those briefings was way back in 2015. Outside of Congress, FDA posted meeting minutes after every negotiation and held public meetings before discussions began to hear feedback on the draft recommendations last fall.

The panel today, representing the manufacturers of drugs and medical devices, and the patients who rely on the products they make, can speak to this process. Each of the industries represented here—prescription drug, generic drug, medical device, and biosimilar—agreed to increase the user fees going to FDA over the next 5 years. I am interested in hearing why this is a good agreement for you and for the companies you represent.

Patients were involved in developing the commitment letters, and we have already begun receiving support from patient groups asking us to reauthorize the agreements expeditiously. For example, the National Organization of Rare Diseases and Friends of Cancer Research wrote to me and to Senator Murray, saying,

> "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 Energy and Commerce Committees for moving forward with these critical mechanisms and look forward to their swift and unimpeded passage."

I also look forward to hearing from the Alliance for Aging Research today on how the user fees benefit patients as they age.

After reviewing the recommendations from industry and the FDA, I believe these are good agreements for patients. I look for-

ward to working with Senator Murray and our other committee members to approve these agreements here in committee and move them to the floor in a timely manner so patients and the agency and the industry can operate with certainty.

Senator Murray.

## OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Well, thank you very much, Chairman Alexander, and all of my colleagues.

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

I am glad we are able to move forward with today's important discussion without the dark cloud of Trumpcare looming over us, at least for now. Millions of families spoke out clearly about how Trumpcare would have been an absolute disaster for them. It would have kicked millions off their healthcare, spiked premiums, gutted Medicaid, and I could go on.

As Democrats on this committee made very clear, had Republicans jammed Trumpcare through the Senate without this committee holding a single hearing, it would have continued this committee's move into partisanship and gridlock, which started with a rushed nominations process, and put at grave risk our ability to work together on shared priorities. I'm very glad that Trumpcare was soundly rejected and that more and more Republicans are finally accepting what so many of us have been saying for years, that we should be working together to make healthcare more affordable, accessible, and higher quality because people are looking to us, particularly at this committee, to come together on real bipartisan solutions.

The issue before us today, the FDA user fee reauthorizations, is a chief example of how we can work together to help patients and families. As we discuss the reauthorizations, I want to make my priorities very clear: upholding a high bar of safety and effectiveness to protect the public health and drive the development of innovative products, and ensuring FDA has the resources to carry out this important work.

A critical part of this is maintaining FDA's gold standard of consumer safety and protection, a standard patients and families have come to trust around the world when making decisions about their health. I hope that's a goal all of us share. I'm glad that today, we will be able to ask key players from the industry about the ways you all can and must step up to the challenges, not only to make sure we develop lifesaving treatments, but also to make sure these treatments are safe and affordable for patients and families.

The finalized user fee agreements for drugs, generics, biosimilars, and medical devices reflect thorough negotiation between FDA and these industries and incorporate input from patient and consumer groups. While Congress should be providing FDA with greater investments to support its critical work, the user fees paid by the industry are essential to supporting FDA's operation and mission. These fees help FDA meet the complex challenges of 21st century technology and the movement toward precision medicine. Especially in today's budget environment, the agreements help ensure the FDA can uphold its gold standard of approval while evaluating new drugs and devices efficiently.

Moving forward with these agreements is absolutely necessary if Congress wants to advance safe, effective, and innovative medical products for patients and families across the country. Without these agreements, the agency would be unable to do its job effectively. I oppose efforts by the Trump administration to take unprecedented actions to alter these agreements or to undermine the important public health work of the agency.

I am also concerned the administration is hampering FDA by depriving it of key staff and blocking its ability to issue the guidance and regulation needed to foster innovation. I was disturbed that the Trump administration went so far as to muzzle the FDA center directors that were before this committee to discuss the user fees 2 weeks ago from being able to discuss the crippling consequences of these dangerous proposals.

Mr. Chairman, I am glad that you and I agree we need to move forward, because these agreements advance several significant priorities. For one, we have restructured the generic fees to help more small businesses compete in the market. We've also put a goal review date on all outstanding generic applications from the backlog and prioritized products that can have the biggest impact on cost for consumers.

For biosimilars, we continue to build the program up and provide greater clarity and support for product developers. We have worked to increase accountability and reduce administrative burden across all the agreements, and these agreements advance many of the policies we passed as a part of the 21st Century Cures Act, like making sure patients' perspectives are considered in drug and device development and advancing the science on biomarkers.

As I have talked about before, we must take additional steps to prioritize consumer safety and protection by increasing the post-market surveillance of medical devices. The medical device industry produces amazing innovations for patients, and I am proud to have a robust medical device sector in my home State of Washington.

The National Evaluation System for Health Technology, known as NEST, is a project started by FDA and several healthcare industry partners to better harness information from registries, electronic health records, and medical claims to inform product development and safety. While I was pleased that some of the medical device user fees will support this system, I am very disappointed that the medical device industry has explicitly refused to support any post-market safety activities through fees. Patients and families in my home State of Washington and nationwide deserve to know the devices used in their care are safe and effective, and I'm going to continue fighting for this until we get meaningful safeguards in place so we can detect problems early.

Critically, today's hearing is also an important opportunity to discuss the related larger issue of prescription drug affordability in our country. The astronomical cost of prescription drugs is a financial hardship for so many patients and families and communities, and we need to face up to the tough questions. We need to come together across the aisle to address a system that's not working, hurting patients and families, and adding to the increasing cost of our healthcare system.

Mr. Chairman, while drug pricing is outside of the FDA's jurisdiction and the most robust solutions likely involve HHS and CMS, this is something this committee needs to address this Congress. While we work on the user fee reauthorizations, I will continue to work with my colleagues on both sides of the aisle on solutions to address this issue facing too many American families.

These user fee agreements will accelerate implementation of the biosimilars pathway and improve the generic drug approval process. These steps will foster a robust drug marketplace that may help to bring down the price of some high-cost drugs. But let's be clear. Those tweaks alone will not solve the problem. More work is needed outside the FDA context and outside this committee's jurisdiction to address the root cause of high prices, and I will be speaking with you, Mr. Chairman, and Chairman Hatch about where we can address this issue as this and other related legislation moves forward in the weeks ahead.

To conclude, as we all know, this committee has a strong tradition of bipartisan success in these user fee agreements. I'd like to keep it that way, and I'm hopeful we can move beyond the failed Trumpcare proposal and work together to build on the progress we have made in our healthcare system.

I'm confident if we all join together toward the common goal of ensuring our healthcare system works for families and puts their needs first, we can make real progress, move toward a bipartisan discussion draft, and deliver results so many families are desperately waiting for. I've laid out some key principles I will be very focused on to protect and uphold the deep trust families place in the FDA, and, again, I look forward to a robust conversation with our witnesses on these priorities.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray.

Each witness will have up to 5 minutes, and we would appreciate you summarizing your remarks in 5 minutes so we'll have more time for questions. Thank you for coming.

The first witness today is Kay Holcombe. She is the senior vice president for science policy at the Biotechnology Innovation Organization. It's called BIO. BIO is the world's largest trade association representing biotechnology companies, academic institutions, and State biotechnology centers. She served as the lead negotiator for BIO in the Prescription Drug and Biosimilars User Fee negotiations with the FDA.

Next we'll hear from David Gaugh, senior vice president of sciences and regulatory affairs at the Association of Accessible Medicines, AAM, formerly the Generic Pharmaceutical Association. AAM is the Nation's leading trade association for manufacturers and distributors of generic prescription drugs. Mr. Gaugh has been with the association since 2012, served as the lead negotiator in the Generic Drug User Fee negotiations. I look forward to hearing how this agreement will streamline approvals, enhance communications, and provide patients with timely access to safe and effective generic drugs.

Third, Scott Whitaker, president and CEO of the Advanced Medical Technology Association, AdvaMed. It's the world's largest medical technology association representing companies producing med-

ical devices, diagnostic products, and health information systems. Mr. Whitaker became President and CEO of AdvaMed last April, and he'll discuss the details of the Medical Device User Fees Agreements.

And, finally, we will hear from Cynthia Bens, vice president of public policy at the Alliance for Aging Research. The Alliance is the leading nonprofit organization dedicated to accelerating the pace of scientific discoveries to improve the human experience of aging and health. Ms. Bens has been with the Alliance since 2006 and led the Alliance through the patient and consumer discussions.

Thanks to each of you.

Ms. Holcombe, let's begin with you.

**STATEMENT OF KAY HOLCOMBE, SENIOR VICE PRESIDENT FOR SCIENCE POLICY, BIOTECHNOLOGY INNOVATION ORGANIZATION, WASHINGTON, DC**

Ms. HOLCOMBE. Chairman Alexander, Senator Murray, and members of the committee, thank you for the invitation to BIO to participate in this hearing.

Since the enactment nearly 25 years ago of PDUFA I, it has become clear that user fees are a critical adjunct to FDA's appropriations. They allow enhancements in review activities that result in faster availability of new products for patients. After this committee developed and Congress enacted the Biologics Price Competition and Innovation Act to establish a new pathway for biosimilars to enter the U.S. market, you also acted promptly to authorize user fees through the Biosimilars User Fee Act.

BIO strongly supports the timely reauthorization of PDUFA and BsUFA. A delay, renegotiation, or failure to reauthorize these programs well in advance of their current September 30 expiration date would have significant negative consequences for FDA, for fee payers, and, most importantly, for patients who need timely availability of safe and effective new drugs and biologics and biosimilar products.

PDUFA changed the landscape of FDA review time. Today, FDA is among the most efficient of all global regulators, and the majority of new drugs are available to U.S. patients first in the world. This was achieved without in any way compromising FDA's gold standards of safety and effectiveness.

Review times are just the tip of the iceberg and are not the reason that patients are waiting. Product development programs are complex, costly, and most do not succeed. The goals of PDUFA VI are focused on that issue, and we believe are transformative for drug development. They include activities to improve the efficiency of drug development through the use of modern tools.

Some of the PDUFA VI goals reflect concepts also included in the 21st Century Cures Act: patient-focused drug development; qualification and use of biomarkers, including the use of biomarkers as surrogate endpoints; evaluating the use of innovative clinical trial designs and nontraditional statistics; real-world evidence for both safety signal determination, which is already done, and to augment clinical data in effectiveness determinations; and computer modeling to inform clinical trial design and to augment clinical data. In PDUFA VI, the evaluations of these new tools will be done in

consultation with the public and with defined goals and reporting requirements.

The progress of BsUFA will also continue. Under BsUFA, FDA has been able to advance biosimilars in the United States. Although there have only been four biosimilar products approved to date, there are now over 60 development programs to 20 different biological reference products. Seminal to these efforts are the communication between biosimilar developers and the FDA through their product development meetings. In addition, FDA, under BsUFA II, will build in additional communication opportunities during the review process for biosimilars.

In both PDUFA and BsUFA, significant steps will be taken to improve the financial management programs and to improve the hiring processes at FDA.

In conclusion, I want to reiterate BIO's strong support for these PDUFA and BsUFA programs. They have served the public well, and they have worked in the best interest of patients.

Thank you, Mr. Chairman.

[The prepared statement of Ms. Holcombe follows:]

PREPARED STATEMENT OF KAY HOLCOMBE

SUMMARY

BIO strongly supports the timely reauthorization of the Prescription Drug User Fee Act and Biosimilars User Fee Act programs (PDUFA VI and BsUFA II). A delay, re-negotiation, or failure to reauthorize the programs well in advance of their current expiration date, September 30, 2017, would have enormous negative consequences for FDA, for fee payers, and—most importantly—for patients who need timely availability of safe and effective new drugs and biologics and biosimilar products.

History tells us that user fees work. Since its first enactment, PDUFA—the grandfather of them all—has changed the landscape of FDA review time, making FDA review efficiency the best in the world. Today, the majority of new drugs are available to U.S. patients first in the world.

But review times are just the tip of the iceberg, and not the reason that "patients are waiting." Product development programs are lengthy, complex, costly, and very high risk—most do not succeed. But experience shows that earlier and better communication between FDA and sponsors can improve the chance of success, and goals of both PDUFA and BsUFA focus on improving both formal and informal communication. Because biosimilars developers were entering a new pathway for FDA, BsUFA I included a series of Product Development meetings before application submission. These will continue. In addition, FDA will initiate, in BsUFA II, an approach to review that builds in additional opportunities for FDA-sponsor communication. This approach has existed in PDUFA since PDUFA V, and will continue. It has been determined by a third-party evaluator to be successful in increasing the numbers of first-cycle approvals. In addition to formal meeting opportunities, additional less formal but critical communication practices were initiated in PDUFA V and will be enhanced and evaluated in PDUFA VI.

The goals of PDUFA VI also focus on making drug development more efficient using concepts additionally included in the 21st Century Cures Act—incorporating 21st century tools such as patient-focused drug development, biomarkers, innovative clinical trial design, non-traditional statistics, real-world data, and computer modeling to augment clinical data.

In both PDUFA VI and BsUFA II, steps will be taken to improve the financial management of the programs, in a transparent way, to ensure long-term viability of these crucially important programs. In addition, changes in hiring processes, incorporation of hiring goals in the goals letters and annual performance reports will give the public a line of sight into hiring of essential personnel, in the event problems occur, such as sequestration or hiring freezes, that will prevent FDA's achievement of its user fee goals. User fees paid by biosimilars and new drug and biologics developers fund the FDA staff who review applications and carry out the performance goals. If FDA is unable to make these hires, user fees cannot be spent. This is not good for fee payers, FDA, or patients waiting for approved therapies.

Chairman Alexander, Senator Murray, and members of the committee: BIO appreciates the opportunity to speak with you today about the reauthorization of the Prescription Drug User Fee Act (PDUFA) and the Biosimilars User Fee Act (BsUFA) programs. BIO strongly supports this fifth reauthorization of PDUFA and second reauthorization of BsUFA and urges timely congressional action on both.

I am Kay Holcombe, 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 user fee programs. Many of them recall the time before enactment of PDUFA I—the grandfather of FDA user fee programs—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. That situation was changed by the willingness of Congress to work with FDA, industry, and others to determine if, and how, review times could be reduced significantly through providing for user fees to support the additional FDA staff needed to carry out more quickly the activities related to review of human drug applications.

PDUFA I proved this could be done. By the end of the 5 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.

The successes of PDUFA gave rise to user fee programs to achieve greater efficiency in the review of medical devices, generic drugs and biosimilars. In the history of biosimilars user fees, this committee features prominently. You developed and took the first congressional action on legislation that became the Biologics Price Competition and Innovation Act (BPCIA), which established the FDA biosimilars program. Recognizing the need for user fees to support that program, you began and executed the process that led to the Biosimilars User Fee Act (BsUFA). This young user fee program has been essential to ensuring that biosimilars would be developed and, although a small number of products has been approved, we believe the program is growing and will continue to grow.

Modifications of both the PDUFA and BsUFA programs, negotiated by FDA and the biopharmaceutical industry with support and input from patient, consumer, and healthcare provider organizations and other stakeholders, are designed principally to improve efficiency, reduce administrative burdens, enhance program long-term sustainability, and ensure that 21" century tools are used to the greatest advantage in the review of new drugs and biologics and of biosimilars—while maintaining the U.S. gold standard of safety and efficacy.

The vision of these user fee agreements is also the vision of 21st Century Cures—patients come first. Key components of both BsUFA and PDUFA are designed to achieve the goal of ensuring that patients have new drugs and biologics as quickly as possible; that timely and efficient processes allow patients access to biosimilars, which expand their choices for treatment; and that focus on good communication between FDA and sponsors results in reduced development times, so unmet needs can be met as soon as possible.

## PDUFA VI

### 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.

## MAKING A DIFFERENCE FOR DRUG DEVELOPMENT = MAKING A DIFFERENCE FOR PATIENTS

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. 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. Other changes also have been supported by user fees: enhancement in the efficiency and effectiveness of FDA's 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 8 months (many such priority applications are completed in fewer than 8 months) and of Standard applications in 12 months. These timelines are now the global gold standard for regulatory efficiency. Our U.S. economy has benefited from PDUFA, because drug and biologic applicants now have greater certainty of a reasonable timeline for completion of their applications, facilitating and encouraging investment in new biopharmaceutical R&D and increasing the number of good-paying jobs in the biopharmaceutical industry. Most importantly, though, patients have benefited. Before PDUFA, U.S. patients legitimately could say that their counterparts elsewhere in the world had new treatments available before they did. That largely is not the case anymore.

FDA's application review time of fewer 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 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 regulatory processes have not kept up with the advancing science.

During the lengthy period of development, 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 might reduce drug development times. How can PDUFA resources be applied to address lengthy, expensive, and 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.

The question facing PDUFA VI stakeholders and FDA was the question that faced this committee as it embarked on 21st Century Cures: What more can be done to change the course of drug development and to reduce the time it takes to get to the 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 Cures proposals and PDUFA VI commitments that would allow these tools to be used most effectively. In both cases, the goal was to ensure more timely availability of new drugs for patients by reducing the time and increasing the chance of success of drug development.

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 staff necessary to carry out the historic commitments of this agreement.

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 through a step-wise approach, with stakeholder input.

The goal of this process can be described as converting largely qualitative information to quantitative information that can have clear application to determining evaluating the benefits and risks of a new drug. 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 dropout, which can compromise or even negate the trial results. Finally, FDA will revisit 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 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 possible 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 could receive timely responses to inquiries that might 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. 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. A number of the PDUFA VI goals are synergistic with those of the provisions of 21st Century Cures. One of those goals is implementation of a pilot program to seek and incorporate the input of external experts to assist in biomarker qualification, to verify if the use of such outside experts can make the processes more timely and efficient. FDA also 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 and additional opportunity for drug developers to discuss their development programs with FDA.

*Using Real-World Evidence*

The Sentinel system, established by FDA in response to congressional direction, is the source of enormous amounts of 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 investigation 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 all 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 potential uses of such real-world data in regulatory decisionmaking. One possibility is that large databases might 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 postmarketing 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 decisionmaking 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 bring-

ing 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 may not always be the most efficient or necessary approach. With new ways of thinking, and given new approaches to statistical analysis, are there better ways to conduct 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 begin answering 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 guidances 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 human drug development.

*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 to 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 successful and are reducing the time of drug development.

PROGRAM SUSTAINABILITY AND FINANCIAL TRANSPARENCY

PDUFA finances and personnel form the foundation that keeps the PDUFA program viable. Since 2002, the PDUFA program has grown at an average of 11 percent per year; this is unsustainable moving into the future. Changes that address the fee collection structure to increase predictability and efficiency and to reduce administrative costs for both FDA and companies will lead to a lower and more sustainable growth rate. These include reducing the volatility of fee collections, eliminating complicated collection and other financial mechanisms that are difficult to administer, improving predictability of annual total revenue collection, and reducing variation of collections year over year. 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 percent of the annual fee collections; and
• reduce the percentage that application fees contribute to the total from the current 33 percent to 20 percent, 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, changing the basis for calculating annual workload adjustments, and developing a 5-year financial plan and updating annually 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.

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 ideal 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 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 will be a significant component of planning for future resource needs, which will contribute 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 resources that will be needed to assure a continuing efficient and effective human drug review program. This modernization of the time reporting system is under way, with a third-party expert already working with the agency to determine the best approach to development and use of capacity planning.

PERSONNEL MANAGEMENT

Hiring and retaining the expert staff essential to carry out user-fee-funded activities is critical for PDUFA VI to succeed. 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 compared to similar positions in the private sector. The 21st Century Cures Act, in which this committee played a significant role, 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 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.

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 drug and biologics applications. This hiring in fiscal year 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 timely allocation of some PDUFA V resources. The hiring of these staff will continue in the first several years of PDUFA VI, along with hiring of additional staff essential to carry out the new performance goals of PDUFA VI.

The negotiated number of FTEs (full-time equivalents) necessary to carry out the goals of PDUFA VI is 230, hired over the years of the user fee agreement, fiscal year 2018 to 2022. These include medical reviewers, pharmacologists, pharmacists, chemists and other scientific experts, biostatisticians, financial managers, and other essential staff. For the first time, hiring goals are included in the PDUFA VI Performance Goals Letter, and FDA will report on its progress in meeting these hiring goals in each year's performance report, beginning in fiscal year 2018.

## BsUFA II

### OVERALL GOALS FOR BSUFA II

As we did to develop our approach for PDUFA VI, BIO worked with our members to define our overarching goals. First, we want to ensure that FDA will have the resources, including human resources, over the next 5 years to accomplish the objectives of the BsUFA program, including timely and efficient review of biosimilars applications and further clarification and enhancement of the processes and tools the agency uses to regulate biosimilars. Second, as for PDUFA, we want to improve the transparency, financial accountability, and sustainability of the BsUFA program. We believe the BsUFA FDA-industry-stakeholder reauthorization proposal transmitted to Congress in December 2016 meets these two goals, and we strongly support its timely enactment.

### WHAT HAS BEEN ACCOMPLISHED DURING BSUFA I?

To inform our thinking, we looked at what FDA has accomplished in the first 4 years of the BsUFA program and reviewed the third-party assessment of the costs and workload associated with activities related to the review of biosimilar applications and the development of policies and procedures to implement the new biosimilars program.

During just the first 3 years of BsUFA I, the time period examined by the independent third party, FDA held 127 biosimilar product development meetings with sponsors. As of 2015, there were 57 biosimilars development programs under way—a number that has continued to increase.

FDA has issued five final Guidance documents to assist sponsors and other stakeholders to understand some of the agency's thinking about how the new biosimilars pathway would work and about the agency's expectations regarding the kinds of studies and data that would be required for biosimilars approval. FDA also issued final Guidance on naming for biosimilars and innovator biological products. This was a particularly important document, because FDA needed to take an approach to biosimilars names that would provide clarity for prescribers and patients and assist pharmacovigilance, but not suggest, by virtue of a naming convention, that some products may raise safety or efficacy issues that do not exist.

FDA also has issued an additional five Guidance documents that remain in draft, including the recent draft Guidance regarding FDA's views on determining interchangeability. BIO has urged FDA to lay out its thinking on interchangeability, so we are pleased that a draft is available for public comment. We hope the agency will finalize this draft as quickly as possible after the public comment period ends. Many stakeholders believe it is crucial for FDA to explicate its expectations for the data needed to determine that a biosimilar product is interchangeable with its reference biological product, which the statute defines as a biosimilar that can be substituted for, or switched with, the reference product with no adverse impact on any given patient's clinical outcome. Such a determination, many believe, may serve to encourage greater prescribing and use of biosimilars as the availability of biosimilar products increases, provided the determination is sufficiently rigorous.

Beyond issuing these Guidance documents, FDA has committed substantial time and resources to make the pathway to approval for biosimilars viable and credible. Because of both the complexity of the products and the novelty of this category of "highly similar" or "interchangeable" products, we recognize that these early years necessarily have been a time of learning and building within the agency. Although four new biosimilars approved since enactment of the BPCIA and the initiation of BsUFA may seem like a small number, we are confident that the program—and the availability of biosimilars—will grow as the agency builds expertise and capacity.

In fact, as FDA has reported in its annual BsUFA Performance reports, and as an independent contractor also has documented, the number of meetings between FDA and sponsors planning or executing biosimilars development programs has increased substantially since the program began. As of October 2016, based on meetings between FDA and sponsors, there are 66 biosimilar development programs under way, to develop biosimilars to 20 different reference biological products. Of

course we do not know what percentage of those programs will result in applications, or which applications will be approved. The numbers certainly demonstrate the upward trend for which supporters of biosimilars have hoped.

WHAT CAN BE ACCOMPLISHED DURING BSUFA II?

BIO worked with FDA and other industry organizations representing biosimilars developers and innovators, with input from many other stakeholders such as patient organizations and healthcare providers, to develop detailed proposals for continued progress and enhancements during BsUFA II. These proposals are encapsulated both in the legislative language proposed to this committee and in the Biosimilar Biological Product Authorization Performance Goals and Procedures for Fiscal Years 2018 through 2022. Among the commitments included in the BsUFA Goals Letter are the following.

*Review Timelines*

First, FDA agrees to meet defined timelines for its reviews and decisions regarding biosimilars applications. Specifically, for 90 percent of original applications, a decision will be made within 10 months of the date on which the application is officially accepted for review by the agency. How well FDA does in meeting this timeframe, like others for re-submitted applications and supplements, will be reported annually and publicly by the agency. These goals mirror those of the PDUFA program.

*Meeting Management*

FDA-sponsor meetings before an application is submitted have been a key part of BsUFA and an essential component of a concerted effort to stand up for this new program. These are formal opportunities for sponsors to discuss their development plans and approaches with the agency reviewers and receive technical assistance regarding ways to proceed that will give the development the highest chance of success. Under BsUFA I, there was agreement that user fees would be associated with these meetings; that will continue under BsUFA II. It is a long-term goal we share with FDA that these Biosimilar Product Development meeting fees eventually will be phased out, based on the agency's ability to meet its annual target revenue for the BsUFA program, and to meet its performance goals, with fees assessed on biosimilars applications and products—as is the case in the PDUFA program. This will require a more significant increase in the number of applications and products than is expected over the next 5 years.

Some enhancements to the formal meeting processes also are among the performance goals for BsUFA II. These have the purpose of ensuring that requirements for both FDA and sponsors, in terms of response times, meeting times, and documentation, are reasonable to allow for the best and most productive meetings and the most timely and useful advice for sponsors.

*New Review Program*

A new approach to the review of biosimilars applications will be implemented during BsUFA II, modeled after the "new NME" program of PDUFA. The goal of this program is an increase in the number of first-cycle approvals—saving time and money for sponsors and, importantly, making approved products available to patients as efficiently as possible. The program provides applicants with new opportunities, during the course of the review, to receive updates and advice from FDA about how the review is proceeding and what additional information might be needed. If there are questions or concerns, the applicant will have a chance and the time to respond—avoiding last-minute problems that cannot be resolved adequately in the time remaining before the BsUFA deadline.

Based on an independent third-party review, the PDUFA new NME program has been highly successful in the view of both the FDA and sponsors. Importantly, this approach has achieved its intent to increase the number of first-cycle approvals. In short, this means there is a higher chance that an application entering FDA in month one will exit, approved, in month 12. The chance that the 12-month timeline will be extended, or that the application will need to be submitted for a second review cycle, is greatly reduced.

The expectation for BsUFA Ills that results will mirror those that have been seen for new drug and new biological license applications. In other words, more and more productive communication between FDA and sponsors will lead to less overall time to product approval.

Under the new program, the applicant is encouraged to meet with the FDA review team to discuss the content of the planned application in advance of the submission. Once the complete application (as agreed at the pre-submission meeting) is accepted

for review by the agency (60 days), a 10-month count-down begins. At approximately mid-cycle, FDA will arrange a mid-cycle meeting with the applicant—in most cases by telephone—during which appropriate review team members will update the status of the application and identify any concerns or questions, discuss the review team's thinking about possible post-market requirements, and provide the applicant with upcoming milestone dates such as advisory committee meetings. If an advisory committee is planned, it will be scheduled at least 2 months before the end of the 10-month review time.

A second, late-cycle meeting will be held no later than 12 days before any planned advisory committee meeting. At this meeting—usually a face-to-face meeting—FDA and the applicant will discuss any major deficiencies in the application, the agency's views on the submitted data and any additional data that may be needed, manufacturing issues, inspectional findings, any proposed post-market requirements, and any issues FDA plans to raise with the advisory committee. This timeframe will provide the applicant more than 2 months before the BsUFA goal date to work with FDA to resolve outstanding issues—a meaningfully longer time than frequently was the case previously. If there is no advisory committee planned, the late-cycle meeting will occur no later than 3 months before the BsUFA goal date.

The establishment of this new review approach is significant for several reasons. First, it provides clear, guaranteed, important opportunities for applicants to know what is happening with their reviews—in a timely way that allows them to have meaningful input and an opportunity to address problems and concerns. Second, it provides timeframes for various steps in the review process that are publicly reportable through FDA's BsUFA annual Performance Reports. While we expect that this Program will be as relevant and helpful as it has been in PDUFA, it is critical that, given the inherent differences between the development and approval processes for new biological products and biosimilars, an independent third-party evaluation of this new biosimilars review program be undertaken. The Goals Letter lays out specific components of the evaluation. The evaluator will look not only at how the program is working and whether it is achieving its aim of more first-cycle approvals, but also at the question of whether and to what extent the earlier Biosimilar Product Development meetings, for which applicants also pay user fees, could have or should have identified issues that subsequently may be raised at a mid-cycle or late-cycle meeting during the review. The third-party evaluator will submit both an interim and a final assessment of the program, by the end of 2020 and by June 2022 respectively. These reports will be published for public comment, and public meetings will be held on each.

*Guidance*

Stakeholders across the spectrum agree that timely and substantive guidance, particularly in this new program area and for this new approval pathway, is essential to the success of the program. The lack of Guidance leads to uncertainty and missteps that limit or delay the availability of new safe and effective products for patients. Guidance that remains in draft for lengthy periods of time has the same effect. Thus, it is important that goals be set under BsUFA II not only for the issuance of a new Guidance that explains FDA's perspectives in general, as well as with respect to specific biosimilars products or types of products, but also for the finalization of Guidance already issued in draft. Those goals are laid out clearly in the Goals Letter. While meeting these goals—a key publicly reportable user fee commitment—FDA also needs to ensure that the public has ample opportunity to comment on draft Guidance and that such public comment is taken into account in the finalization of any Guidance.

In addition, the Goals Letter provides FDA's commitment to revise and update the Good Review Management Practices Guidance and general guidance relating to processes, procedures, and timelines for meetings between FDA and sponsors, both of which apply to NDAs and BLAs, to include and specifically reference biosimilars.

Finally, the Goals Letter includes FDA's commitment to continuing to clarify the biosimilars review pathway and provide information important to sponsors of both biosimilars and innovator biological products. This includes, for example, revision or re-issuance of Guidance relating to the so-called "transition" products; harmonization of varying definitions of "biological product;" and updating of the "Purple Book" with information including the date of first licensure of potential reference biological products.

*Program Sustainability and Financial Transparency*

BsUFA will benefit from the modernized time reporting and new capacity planning efforts that are also part of the PDUFA VI goals, as these changes are being implemented across the Centers for Biologics (CBER) and Drugs (CDER). By stat-

ute, FDA staff who conduct the activities related to the review of biosimilars applications are the same as those who review applications for approval of new drugs and new biological products. Therefore, modernized time reporting will be as useful for determining resource needs for BsUFA as for PDUFA. Modernized time reporting will provide data that are much more accurate than currently available about the time and resources required to complete the various tasks associated with application review. In addition, the modernized system will ensure accurate allocation of time and resources to BsUFA activities and to PDUFA activities.

Having this information also will allow FDA, for the BsUFA as for the PDUFA program, to plan for the capacity necessary to meet the needs of future years.

To assist in the development of a capacity planning function, an independent third party will evaluate various options and make recommendations regarding the best ways for FDA to assess its resource needs on an ongoing and forward-looking basis, for all CDER and CBER review-related activities. The specific tasks associated with the review of biosimilars applications will be built into this assessment. As with all other BsUFA and PDUFA reports and assessments by FDA or by independent contractors, this evaluation will be public, and public comment will be invited and taken into account.

By the second quarter of 2018, FDA will publish an implementation plan for establishing and utilizing a capacity planning function and modernized time reporting, which will include biosimilars review activities specifically.

These activities provide confidence to fee payers and other stakeholders that there is a sound basis on which target revenues and fee amounts are calculated. It has been especially difficult to predict the amount of funding needed for BsUFA, because this is a new-to-the-U.S. industry without a history of development times or application submissions. This will change with time, but until then, the perspectives of experienced independent experts will be essential.

FDA also will include BsUFA resource management in the scope of work for the contractor that will evaluate PDUFA resource management. This evaluation will include an assessment of how the BsUFA program is administered, how the user fee funds are allocated and used, and what changes might be made to improve the governance of the program.

These activities, including the more accurate resource assessments that will be possible from modernized time reporting, will allow FDA to establish an independent BsUFA user fee structure. While elements of the PDUFA structure that enhance financial management will apply, BsUFA will have its own fees not necessarily based on PDUFA fees.

*Personnel Management*

FDA's well-documented hiring difficulties are problems for BsUFA as for PDUFA. Neither of these programs can work without a strong, capable, and skilled FDA that can make timely and science-based decisions in the interest of patients and the public health. We appreciate this committee's efforts, working with the House Energy and Commerce Committee and many other Members of the House and Senate, to include changes in the 21st Century Cures Act that will greatly benefit FDA's hiring capabilities. These changes will provide FDA with some key authorities that it needs to attract the highly educated, experienced, and talented individuals we all want to see working on our applications for approval.

Process improvements are under way already at FDA. Both the BsUFA II and the PDUFA VI agreements include a commitment that FDA will contract with third parties to help implement new processes and to evaluate on an ongoing basis the progress the agency is making. Because all the reviewers in the BsUFA program also are PDUFA reviewers, it is crucially important to the success of the biosimilars program for FDA to meet the significant hiring goals under PDUFA. Even more important is for the agency to put in place sustainable and durable processes and procedures, so this hiring is not merely a 5-year surge, but is a lasting approach that keeps FDA staffed at the level it requires to do its job.

Importantly, all of the activities that will be and already are being undertaken to improve the hiring situation will be public. We all will be able to see the assessment of the third-party evaluator, consider any recommendations, and provide comments to FDA. We also will be able to see the numbers. We do not want FDA to fall behind its hiring goals, because we know that the user fee commitments we rely on cannot be met unless the people are there to meet them. Annual hiring goals are included in the BsUFA agreement as they are in the PDUFA agreement—and the public will be able to see in the annual Performance Reports whether these goals are being met. We want to see what is happening so we can work with this committee and FDA to help stop any downward trend. We believe we share this goal with stakeholders across the spectrum.

In discussing FDA hiring, I also want to reiterate BIO's longstanding views on the potential negative consequences that arise from the sequester of user-fee funds or hiring freezes that can result in FDA's inability to fill vacancies and make new hires that are necessary for meeting its commitments under PDUFA and BsUFA—or, in general, for carrying out its crucial public health responsibilities. User fees paid by biosimilars applicants and by applicants for new drug and new biological product approvals support a significant number of FDA personnel. In particular, they support the staff identified to carry out the program performance goals. If FDA is unable to make these hires, user fees cannot be spent. This is a situation that is not good for fee payers, for FDA, or for patients who are waiting for approved therapies.

To summarize our views on the financial and hiring enhancements of PDUFA VI and BsUFA: BIO believes they are on target and essential to ensure both the long-term viability of these important user fee programs 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 user fee goals and carry out its public health mission.

BIO strongly supported and applauds the enactment of 21st Century Cures, as we strongly support the PDUFA VI and BsUFA II negotiated agreements. These efforts will make a difference for patients.

BIO urges Congress to act swiftly to move the PDUFA VI and BsUFA II authorizations forward. These agreements, negotiated between FDA and the biopharmaceutical industry with input and support from multiple other stakeholders, positively advance our shared goal of making safe and effective treatments available to patients as efficiently and quickly as possible. We shortly will provide a letter expressing our strong support for timely enactment of the PDUFA and BsUFA reauthorizations.

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

The CHAIRMAN. Thank you, Ms. Holcombe.

Mr. Gaugh.

**STATEMENT OF DAVID R. GAUGH, R.Ph., SENIOR VICE PRESIDENT OF SCIENCES & REGULATORY AFFAIRS, ASSOCIATION FOR ACCESSIBLE MEDICINES, WASHINGTON, DC**

Mr. GAUGH. Thank you, Mr. Chairman, Ranking Member Murray, and members of the committee. First, let me thank you for allowing me to participate in this very important hearing. I'm David Gaugh, senior vice president for sciences and regulatory affairs at the Association for Accessible Medicines, AAM. We represent the stakeholders in the generic industry.

Generics represent over 89 percent of all prescriptions dispensed, but only 27 percent of the expenditures on those prescriptions. As such, generic drugs play an ever important role in bringing down the artificially high prices of drugs, thereby keeping medicines within reach for the American public.

I'd like to begin by commending the committee for your continued focus on these important issues that we are going to discuss today. The generic industry's remarkable growth plays a vital role in the lives of the American public every day. This growth in the generic industry has also served to underscore the critically important role of the FDA. As I will highlight, the level of cooperation between industry and the FDA has never been greater.

However, the agency remains underfunded, and the responsibility for ensuring access to safe, effective, and affordable medicines is a shared one for all of us. This is why the generic industry has agreed to provide the FDA with additional resources to address the ongoing challenges.

I'm here to discuss AAM's conviction that the best way of achieving the goal of providing patients access to affordable generic alter-

natives is through the development of policies that promote robust competitive markets. These competitive markets are the best way to control drug costs, and GDUFA II will play a key role in achieving those goals.

The priority of the generic industry in GDUFA II was to achieve a more effective and transparent generic review program. We believe that accomplishment will improve the rate of first-cycle approvals on the earliest legally eligible date through greater transparency and communications with the agency. Thus, both FDA and the generic industry benefit from sharing knowledge and experiences throughout the review.

Our goal was not merely a faster review timeline, but a more effective review process. The fewer review cycles required to get to approval, the sooner patients and payers can experience the benefits of generic competition. We strongly believe that GDUFA II is well-positioned to achieve this goal.

A few key areas within GDUFA that we think are important add-ons to what we've learned from GDUFA I and into the negotiation of GDUFA II is application metrics. FDA will now review and act on 90 percent of all ANDAs within 10 months for standard applications and within 8 months for priority applications. This includes the inspection components of that review process.

There's also a bridging piece that we put in, or what we call No ANDA Left Behind. In GDUFA I, there were several products in the backlog in years one and two that did not get GDUFA goal dates. In GDUFA II, all those applications will have an effective GDUFA goal date assigned to them on October 1, 2017, if they have not already been assigned.

GDUFA II creates a pre-ANDA submission communication pathway for complex products. This is a first in GDUFA. This early engagement between industry and FDA will significantly contribute to the applicant's ability to improve the overall submission quality of ANDAs, which, in turn, will contribute to that first-cycle review process.

The agreement includes increased transparency and communications between the FDA and ANDA applicants through liberal use of information requests, or IRs, and division review letters, DRLs. These enhancements are intended to decrease the number of review cycles and move them toward first-cycle review.

GDUFA II includes several new performance and financial reporting requirements, which we thought were important, to ensure transparency and efficiencies are maintained. The new reporting requirements will allow Congress, industry, and FDA to better assess FDA's resource management planning and processes.

The proposal supports small businesses this time, which was not in GDUFA I, by exempting them from a facility fee until the first ANDA in that facility is approved. The proposal also provides for tiering in the annual ANDA program fee based on small, medium, and large companies. The tiering is based on a total number of approved ANDAs for each company.

With the many enhancements in GDUFA II and which they provide, AMA strongly supports the GDUFA II package, as it provides critical review processes to achieve our stated goals. I'd also like to point out that I was part of the industry's negotiating team for

BsUFA II, and I've provided details of that agreement in my written testimony, and AAM strongly supports the BsUFA II package as well. However, it is important to emphasize that the funding provided by both GDUFA II and BsUFA II are an addition to and not a substitute for congressional appropriations.

In conclusion, Mr. Chairman, the GDUFA and BsUFA user fee proposals are a culmination of months of negotiations between FDA and industry, and the final products as transmitted to Congress represent a careful balance between all stakeholders involved. We respectfully urge the committee to approve GDUFA and BsUFA as negotiated and agreed to between FDA and industry and without changes to the agreement.

Thank you very much.

[The prepared statement of Mr. Gaugh follows:]

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

GENERIC DRUG USER FEE AMENDMENT (GDUFA) II

SUMMARY

Under the program, FDA will receive over $2.6 billion during the 5 years of supplemental funding through industry user fees in order to help the agency expedite access to low-cost generic drugs.

To function most effectively, and to promote the goal of achieving first cycle approvals and approvals on the earliest legally eligible date, industry focused on increasing transparency and communication during the review process. Maximizing the effectiveness of the review process requires the cooperation of FDA and the generic drug industry, both of whom will benefit from sharing their knowledge and concerns throughout the review process. The fewer review cycles to approval, the sooner patients and payors can experience the benefits of generic competition.

The key goals of GDUFA II remain:

**Safety**—Ensure that industry participants, foreign or domestic, who participate in the U.S. generic drug system, are held to consistent quality standard.

**Access**—Expedite the availability of low cost, quality generic drugs by bringing greater predictability to the review times for ANDAs, amendments and supplements.

**Transparency**—Enhance FDA's ability to protect Americans in the complex global supply environment by requiring the identification of facilities involved in the manufacture of generic drugs, active pharmaceutical ingredients, and improving FDA's communications and feedback with industry in order to expedite product access.

OVERVIEW OF PERFORMANCE GOALS

**Application Metrics**—FDA will review and act on 90 percent of complete electronic ANDAs within 10 months after the date of submission for standard applications and 8 months for priority applications. Priority status will be provided by FDA for submissions affirmatively identified as eligible for expedited review pursuant to current CDER Prioritization Policies.

**Bridging**—Prior to the completion of GDUFA I all applications and supplements will be assigned a Target Action Date (TAD) by FDA. Upon implementation of GDUFA II (October 1, 2017), all GDUFA I TADs will be converted to official GDUFA II Goal Dates.

**Complex Products**—GDUFA II creates an optional pre-ANDA submission communication process to provide clarifying regulatory expectations for prospective applicants early in product development. This will aid in the applicants ability to meet FDA's expectation earlier in the drug development phase in order for the applicant to submit a complete ANDA submission which would promote a more efficient and effective ANDA review process and reduce the number of review cycles required to obtain ANDA approval, for complex products.

**ANDA Review Transparency and Communications Enhancements**—Increased transparency and communication between FDA and ANDA applicants throughout the review process through liberal use of Information Requests (IRs) and Division Review Letters (DRLs) to decrease the number of review cycles, post-CRL

teleconferences with metrics, timely tentative approval conversion into full approval, and metric dispute resolution process.

**Reporting and Accountability**—FDA will conduct increased financial and performance reporting to maximize transparency. Financial transparency and efficiency will be ensured by FDA's commitment to conduct activities to evaluate the financial administration of the GDUFA program to help identify areas to enhance operational and fiscal efficiency. Several key performance reporting requirements are also in place to ensure transparency and efficiencies are maintained with the type and level of reporting by quarter and annual.

OVERVIEW OF FEES

The additional user fee funding is an inflation-adjusted $493.6 million annually for each of the 5 years of the program.

The distributions of the fees are in two categories.

(1) Per submission fee or one-time fee comprised of:

- ANDA application fee (33 percent).
- DMF application fee (5 percent).

(2) Annual fee including the facility fee and the ANDA and API Program fees:

- The facility fee is divided into ***API-owned*** (7 percent) and ***ANDA-owned*** (20 percent) facilities, CMO-owned facilities (6 percent) are a subset of the ANDA facilities (offering an additional small business consideration).
- The Program fee is assessed for DMF and ANDA holders are at 7 percent and 35 percent respectively.
- Additionally, the ANDA program fee is tiered into small, medium, and large categories.

**Where Do We Stand on the Backlog?**—GDUFA I required "action" on 90 percent of the pre-GDUFA I (Pre-10/1/2012) workload, often called the backlog. FDA has met the goal and acted on more than 90 percent of the backlog to date.

- An action is categorized as one of the following: approval, tentative approval, refuse-to-receive, complete response, withdrawal or denial.

GDUFA II has no submission left behind—all ANDAs and amendments will be given a review goal.

- Includes both new submissions and submissions from GDUFA I and pre-GDUFA I.

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Good morning Chairman Alexander, Ranking Member Murray, and members of the Committee on Health, Education, Labor, and Pensions. First, let me thank you for asking me to participate in this timely and important hearing.

I am David Gaugh, senior vice president for Sciences and Regulatory Affairs at the Association for Accessible Medicines (AAM), formerly GPhA, and the Biosimilars Council (Council) and a licensed pharmacist. AAM represents the manufacturers and distributors of finished generic pharmaceuticals, bulk pharmaceutical chemicals, and the suppliers of other goods and services to the generic industry. Generics represent greater than 89 percent of all prescriptions dispensed in the United States, but only 27 percent of expenditures on prescription drugs.

The Biosimilars Council, a division of AAM, works to ensure a positive regulatory and policy environment for biosimilar products, and educates the public and patients about the safety and effectiveness of biosimilars. We are deeply committed to accessible, affordable and high quality medicines.

INTRODUCTION

I would like to begin today by commending the committee for your continued focus on the important issues we will examine today. As someone who has worked in and around the generic drug industry for more than two decades, I have witnessed firsthand the industry's remarkable growth and the vital role it plays in the lives of Americans every day, by providing access to affordable generic medicines.

As for the biosimilars industry, I have been engaged in this industry for over a decade and have seen American ingenuity take this science to new levels. Today we have a growing and thriving biosimilars industry—creating jobs and leading the world with our innovative science.

This growth in both the generic and biosimilar industries has served to underscore the critically important role of the Food and Drug Administration (FDA). As I will highlight, the level of cooperation between industry and the FDA has never

been greater, and it is our hope that this collaboration will continue throughout all of our interactions with the agency.

However, the agency remains underfunded, and the responsibility of ensuring access to safe, effective and affordable medicines is a shared one with the entire pharmaceutical industry. That is why the generic and biosimilar industries have once again committed to provide the FDA with additional user fee resources to address the ongoing challenges caused by an increasingly global drug supply chain.

GENERIC USER FEE AMENDMENT

I am here to discuss AAM's conviction that the best way of achieving the goal of providing patients access to generic alternatives is through the development of policies that promote robust, competitive markets.

Generic manufacturers make complex and highly confidential analysis when selecting which products to pursue. This analysis can include assessing the complexity in reverse engineering, the State of the intellectual property, the size of the market, the likely number of competitors, the product development and manufacturing capabilities and costs.

Because of these complexities, AAM believes that the best way to control drug costs generally, is through policies that incentivize competition and the Generic Drug User Fee Amendment (GDUFA II) does just that.

GDUFA II builds on the experiences—both the successes and shortcomings—of GDUFA I. The priority of the generic drug industry in the GDUFA II negotiations was to achieve a more effective and transparent generic drug review program. We believe that accomplishing this goal will improve the rate of first-cycle approvals on the earliest legally eligible date through greater transparency and communication during the review process. Greater communication and cooperation between FDA and generic drug sponsors benefits both parties by sharing knowledge and experiences throughout the review process. Our industry's goal was not merely a faster FDA review timeline, but a more effective review process—that enables more approvals during the first-review cycle. Similar to the goals of the branded drug user fee program, PDUFA, reducing multiple FDA review cycles is a critical component of increasing access to affordable generic alternatives. The fewer review cycles required to get to approval, the sooner patients and payors can experience the benefits of generic drug competition. We strongly believe GDUFA II is well-positioned to achieve this goal.

**A few key areas of focus in GDUFA II include:**

*Application Metrics*—FDA will review and act on 90 percent of ANDAs within 10 months after the date of submission for standard applications and 8 months for priority applications. This includes the inspection components of the review process. Priority status will be provided by FDA for submissions affirmatively identified as eligible for expedited review pursuant to current CDER Prioritization Policies (MAPP 5240.3 Rev. 2).[1]

- Submissions containing patent certifications pursuant to 21 CFR 314.94(a)(12);
- Submissions related to drug shortages;
- Submissions that are subject to special review programs such as the President's Emergency Plan for AIDS relief;
- Submissions related to public health emergencies;
- Submissions related to certain government purchasing programs;
- Submissions subject to statutory mandates or other legal requirements;
- Supplements for which expedited review is requested under 21 CFR 314.70(b)(4); and
- Submission for "sole-source" drug products.

*Bridging (No ANDA Left Behind)*—In GDUFA I, ANDA applications that were filed with the FDA prior to October 1, 2014, did not receive an official GDUFA I Goal Date. However, during early implementation phases of GDUFA I, the FDA agreed to assign Target Actions Dates (TADs) to those applications. These TADs would allow both the FDA and industry to better track the application status. During GDUFA II negotiations, it was agreed that ALL GDUFA I pending applications would be provided an official GDUFA II Goal Date. Therefore, prior to the completion of GDUFA I, all applications and supplements that have been assigned TADs by FDA will be converted to official GDUFA II Goal Dates. For all applications and supplements that were either (a) previously not assigned a TAD or (b) were previously assigned a TAD and the TAD was missed, at the time of GDUFA II com-

[1] Center for Drug Evaluation and Research, MaPP 5240.3 Rev. 2, *https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf*.

mencement, these pending applications will be assigned a goal date by the FDA that shall not be later than July 31, 2018. This will provide for an official accountability for all pending application.

*Complex Products*—The GDUFA II agreement creates a pre-ANDA submission communication pathway for a subset of generic drug applications, complex products. Like the Breakthrough Therapies program initiated for certain high priority branded drug application, earlier interaction between the applicant and FDA is expected to enhance industry's ability to understand and anticipate FDA's expectations during the critical research and development phase for complex products. With this new pathway, industry and FDA will be able to engage in product development, pre-submission, and mid-review cycle meetings for complex products. As captured in the commitment letter, industry will need to meet a high bar in order for FDA to grant a meeting request. The high bar was deliberately set to allow FDA to staff up in the earlier years, which is reflected in the metrics in GDUFA II. It is industry's belief that this early engagement between industry and FDA will significantly contribute to the applicant's ability to improve the overall submission quality of ANDA's, which in turn will contribute to first-cycle approvals.

*ANDA Review Transparency and Communications Enhancements*—The agreement includes increased transparency and communication elements between FDA and ANDA applicants throughout the review process through liberal use of Information Requests (IRs) and Division Review Letters (DRLs). These enhancements are intended to decrease the number of review cycles from the 3–4 review cycles experienced today, and move them more toward first-cycle approvals. FDA should consider how it can further enhance communication with generic drug sponsors to improve on its 9 percent first-cycle approval rate.

*Reporting and Accountability*—FDA will conduct increased financial and performance reporting to maximize transparency to Congress, industry and the public. The GDUFA II agreement includes several new performance and financial reporting requirements to ensure transparency and efficiencies are maintained. The new reporting requirements will allow Congress, generic drug sponsors and FDA to better assess FDA's resource management planning and processes to ensure the overall success of the GDUFA program. The quarterly and annual reporting requirements will also provide insight into the financial and performance efficiencies of the FDA, allowing for future program improvements and enhancements.

*Small Business Consideration*—The GDUFA II agreement supports small business by exempting them from a facility fee until the first ANDA in that facility is approved. The proposal also provides for tiering of the annual ANDA program fees based on small, medium and large companies. This tiering is based on the total number of approved ANDAs for each company.

BIOSIMILAR USER FEE ACT

Biologic medicines are often the only lifesaving treatments for many of the most severe diseases encountered by patients today. In many respects, they represent the future of medicine. Their high price tag, however, can keep them out of reach for many patients.

In October, the FDA reported that over 66 biosimilar programs were under review for development of 20 different biologic products. This was made possible by the BPCIA, and by BsUFA I user fee funding. We learned in BsUFA I, however, that the innovation involved in biosimilar development—the science of understanding what is in a biologic for comparison purposes—is complicated and involves many new skills that the industry and the FDA need to understand. This requires new staff and training to assure high quality and efficient review. Historic FDA staffing cannot meet these needs which depend far less on clinical data, and far more on new innovative scientific techniques that demonstrate that a biosimilar is highly similar to the reference product and has no clinically meaningful differences.

In addition, even more innovation is underway to allow for approval of interchangeable biologics which can be shown to perform the same in any given patient and, when approved, substituted at the pharmacy like generic drugs. This innovation is what makes biosimilars competitive, affordable, safe and effective for patients.

These innovations squarely depend on having the critical additional FDA resources funded by BsUFA II.

Innovation was used to craft the BsUFA II commitment letter. We took a hard look at the first 5 years. Not only are new FDA resources needed, more efficient regulatory approaches that use funding more wisely are necessary to accelerate FDA review. Together we included innovations from BsUFA I and PDUFA to enhance the

review process and to ensure regulatory clarity. The BsUFA II user fees are now tied to the level of resources needed and adjust with resource demand.

Biosimilars provide a cost-saving alternative for patients. BsUFA II will support the foundations set in BsUFA I and provide FDA with adequate resources to apply consistent regulatory standards to all biosimilars, review new applications as they are filed, and develop important public policy positions. FDA, industry and patients will all benefit from the user fee program by gaining a higher degree of certainty in the timeliness of application reviews.

**BSUFA II includes several important enhancements:**

*Review timelines*—Industry agreed to shift review timelines from the current 10-month timeframe to 12 months in order to improve and increase opportunities for communications touch points between industry and FDA, striving for first-cycle review when possible.

*Additional Funding*—Funding will focus on hiring additional staff for guidance development, reviewer training, and timely communication. BsUFA II will not be linked to PDUFA fee levels in order to create independent and predictable funding levels based on program needs and resource requirements.

Draft Guidances—FDA also agreed to publish draft and final guidance documents on several critical, outstanding policy positions.

*Communications*—Enhanced communication and meeting opportunities that eliminate unnecessary delays in development and review. The meeting deadlines were adjusted based on BsUFA I experience to allow for the most effective use of the meetings to accelerate program development. Initial Advisory meetings were accelerated, and Type 2 meetings were extended to allow the Agency to have the time to provide complete answers and better guidance. At the same time an option for written advice was added which could accelerate in many situations the time to receipt of Type 2 meeting advice.

*Resource Capacity Planning*—Using resource capacity planning to set budgets, staffing levels and fees. The use of capacity resource measurement and planning will help ensure that the level of funding is actually tied to the resources needed and will allow for adjustment of fees up and down as the number of programs fluctuate. This should make the review more efficient, avoid the opportunity cost of delays, and allow for adjustment of fee allocation to the kinds or resources actually needed by the Agency. For example, as the number of marketed products increase, the fees will increase and fees may be reduced on the pre-application development side.

*Program Review Models*—Adopting the highly effective Program Review Model to increase first-cycle application approvals and training of review teams for greater effectiveness. The Program Review Model was tested in PDUFA and puts in place performance obligations, communication commitments, pre-filing meetings, mid-cycle communication and a late-cycle meeting. Experience shows that the enhanced communication conserves FDA resources and applicant resources and has enabled first-cycle approval more often than when it was not in place. This should accelerate approval of high quality applications.

*Dedicated Staff*—The agreement makes commitments to dedicate staffing and to issue regulatory guidance to promote best practices and predictability.

*Education*—The agreement expands biosimilar public education activities.

Each improvement accelerates high quality development and review to help assure that patients have more timely access to life-saving, affordable, safe, and effective biosimilars.

SUMMARY

By designing both of these user fee programs to spread fees across multiple stakeholders and sources to keep individual amounts as low as possible, the programs will help assure that patients continue to receive the significant cost savings from generics and biosimilars. It is also important to emphasize that the funding provided by both of these user agreements is in addition to, not a substitute for, congressional appropriations. Expenditure is contingent, as in the past, on a spending trigger tied to congressional appropriations.

CONCLUSION

In conclusion, Mr. Chairman, the user fee proposals are the culmination of months of negotiations between FDA and industry, and the final product, as transmitted to Congress, represents a careful balance among all the stakeholders involved. We respectfully urge the committee to approve GDUFA and BsUFA as negotiated by FDA and industry, without any changes to the underlying agreements. It is also vital that the agreements be approved in a timely manner so that patients,

the FDA, and generic and biosimilar manufacturers can begin to see their many benefits. Nothing is more important to our industries than ensuring patients have access to the safe, effective and affordable lifesaving medications they require, and these historic agreements provide a critical step toward accomplishing this goal. Thank you.

The CHAIRMAN. Thank you, Mr. Gaugh.

Mr. Whitaker, welcome.

**STATEMENT OF SCOTT WHITAKER, PRESIDENT AND CHIEF EXECUTIVE OFFICER, ADVANCED MEDICAL TECHNOLOGY ASSOCIATION, WASHINGTON, DC**

Mr. WHITAKER. Thank you, Chairman Alexander, Ranking Member Murray, and all the members of the committee for the opportunity to testify today on the Medical Device User Fee Agreement. My name is Scott Whitaker. I'm the president and CEO of AdvaMed. We're the leading trade association that works to advance new and innovative medical technologies in order to improve and save lives.

Collectively, the medical device industry works every day to ensure patient access to lifesaving and life-enhancing devices and other advanced medical technologies. I'm very optimistic about what this industry can do for patients if the right policies are in place. I've been encouraged in recent years by the progress at FDA's center under Dr. Shuren's leadership. This progress combined with the provisions of the new user fee agreement and the work that was done by this committee on the 21st Century Cures Act promises to keep things heading in the right direction and strengthen the entire medical technology innovation ecosystem.

The new MDUFA IV agreement lays the groundwork for further FDA performance improvements through five key areas: more ambitious goals, greater patient involvement, important process changes, and increased accountability, all supported by additional resources. I'd like to quickly describe these five areas for you.

First, MDUFA IV goals for total time reviewing a product represents substantial improvement over the current performance. Measuring the total time from submission to an FDA decision to either make that technology available to patients or deny approval is the most meaningful measure of progress.

For 510(k)'s, the total time goal for MDUFA IV will decrease by 13 percent, which returns the total time to historical norms. For PMA products, which are the most innovative, high-risk products, the total time to decision goal will be lowered by 25 percent.

Second, as we all know, patients have a critical voice in product development and evaluation. The MDUFA IV agreement will have increased resources dedicated to supporting patient involvement in the medical device regulatory process.

Third, the agreement includes process improvements that we anticipate will enhance the consistency and timeliness of the review process, independent of specific time goals. One example of a process improvement is that the agreement provides for meaningful pre-submission interactions between the FDA and the companies. Interactions between the sponsor of a medical device application and the FDA, prior to the formal submission of the product application, can provide really helpful guidance that aids the sponsor in ensuring their application contains all the necessary information.

This pre-submission process was first put in place 5 years ago under MDUFA III and has benefited both the industry and the FDA. MDUFA IV builds on this agreement and the success of this program by adding specific time commitments tied to pre-submission meetings, requiring FDA to provide written feedback to companies 5 days prior to that meeting. This provision will help ensure a much more constructive and productive meeting with the FDA.

Fourth, the agreement provides greater accountability. Greater accountability means that FDA's successes under this agreement will be transparent to FDA, to their management, to industry, to patients, and to Congress and the administration so that any problems that arise can be corrected promptly. New reporting tools and two independent management reports will provide key data to track FDA's performance, highlight any failures to meet key goals, and provide a basis for corrective action.

Finally, to give FDA additional tools to meet these goals, the agreement provides additional funds for the FDA. These resources will give FDA what it needs to continue to improve its performance.

Each of these provisions of this agreement has the potential to make a difference in continuing to improve the FDA. But the whole is truly greater than the sum of its parts. Each of the elements of the agreement reinforces the other. Of course, no agreement, no matter how good it is on paper, is self-executing.

Making it work as intended will require the full efforts of FDA's dedicated staff and their managers. Our industry is committed to working with FDA in a way that we can make it a success as well. Continued oversight and interest from Congress will also be critically important. Patients are depending on all of us. The MDUFA IV agreement is good for this industry, it's good for the FDA, and, most of all, we believe it's good for patients.

I thank the committee for the opportunity to testify today and urge you to act promptly to reauthorize this important program.

[The prepared statement of Mr. Whitaker follows:]

PREPARED STATEMENT OF SCOTT WHITAKER

SUMMARY

AdvaMed strongly supports reauthorization of the medical device user fee program, or MDUFA. We believe we are on the right track at FDA's device center, and that recent progress combined with the device-related provisions in 21st Century Cures, plus provisions of this new user fee agreement (MDUFA IV) promise to keep things heading in the right direction to strengthen the medtech innovation ecosystem.

The MDUFA IV agreement is good for industry, good for FDA, and good for patients. We urge this committee and the Congress to act promptly to reauthorize the user fee program and enact this agreement into law. Failure to act would not only jeopardize the critical improvements made by the new agreement but would have a devastating impact on our industry's ability to bring innovative diagnostics, treatments and cures to patients.

The user fee agreement builds the conditions for success in a number of major ways:

- The MDUFA IV goals for total time reviewing a product represent substantial improvements over current performance.
- The agreement will have increased resources dedicated to supporting patient involvement in the medical device regulatory process.
- The agreement includes process improvements that we anticipate will enhance the consistency and timeliness of the review process, independent of the specific time goals.

• The agreement provides for greater accountability.
• The agreement provides $999.5 million (fiscal year 2015 dollars) in user fees for 2018–22. This is built off of a baseline of approximately $679 million from MDUFA III, along with an additional $228 million in new resources to improve the device review process. In addition, there are $92.5 million in one-time costs for items such as IT and infrastructure improvements. Collectively, the resources will give FDA what it needs to continue to improve performance.

Each of the provisions of this agreement has the potential to make a difference in continuing to improve FDA performance. But the whole is truly greater than the sum of its parts. Each of the elements of the agreement reinforces the others.

We are appreciative of efforts by all Members who seek to give the FDA the tools and structure it needs to succeed. Legislative reforms that do not alter the substance of the negotiated agreement between FDA and industry hold the potential to create a legislative reauthorization package that maximizes the opportunity for success at the agency, which should be the shared goal of all involved.

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

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Thank you Chairman Alexander and Senator Murray and members of the committee for the opportunity to testify today.

My name is Scott Whitaker, and I am the president and CEO of AdvaMed, the Advanced Medical Technology Association.

I thank you for convening today's hearing, and for your interest in improving medical device regulation for patients and industry.

## THE U.S. MEDICAL TECHNOLOGY INDUSTRY

AdvaMed's member companies produce the medical devices, diagnostic products, and digital health technologies that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. Our members range from the largest to the smallest medical technology innovators and companies. Collectively, we are committed to ensuring patient access to life-saving and life-enhancing devices and other advanced medical technologies.

I am very optimistic about what this industry can do for patients if the right policies are in place. Fundamental advances in knowledge of human biology down to the molecular level and continued progress in a range of disciplines—computing, communications, materials science, physics and engineering—are fueling innovation, and the potential to save and improve patients' lives is almost limitless.

Patient access to advanced medical technology improves outcomes, enhances care quality, and generates efficiencies and cost savings for the health care system. For example, between 1980 and 2010, advanced medical technology helped cut the number of days people spent in hospitals by more than half and added 5 years to U.S. life expectancy while reducing fatalities from heart disease and stroke by more than half.

I've been encouraged by progress at FDA's device center in recent years, but the innovation ecosystem that supports our industry remains stressed. One key barometer of the health of our ecosystem is the level of investment in startup companies. Unfortunately, we have seen a sharp decline in the number of new medical technology startup companies each year, going from around 1,500 annually 30 years ago to around 600. Since the early 1990s venture capital (VC) investment in the industry has gone from about 13 percent of total VC dollars to about 4 percent in recent years. The time horizon for getting a new innovation from the bench to the bedside remains too long, and as a result investors are looking elsewhere.

## FDA REGULATION OF MEDICAL DEVICES—MDUFA IV

We believe we are on the right track at FDA's device center, and that recent progress combined with the device-related provisions in 21st Century Cures, plus provisions of this new user fee agreement promise to keep things heading in the right direction to strengthen the medtech innovation ecosystem.

The ground-breaking process improvements that were built into the MDUFA III agreement, and the oversight done by this committee, have led to improvements in FDA's regulation of medical devices. FDA has brought down the total time it takes to receive a decision from FDA on a product submission, while still maintaining the strongest standards for evaluating safety and effectiveness. Opportunities for engagement between applicants and FDA throughout the device review process have increased, leading to fewer misunderstandings and false starts, and a better under-

standing of FDA data needs. As a result, the consistency and predictability of the FDA review process has shown improvement.

Additionally, the MDUFA IV agreement follows in the same spirit of the recently enacted 21st Century Cures law, and I thank this committee for its hard work on that bill. Cures included a number of provisions that will improve the predictability and consistency of FDA's device review process, and these are improvements that ultimately lead to greater patient access to safe and innovative products. The MDUFA IV agreement picks up on this theme and includes complementary process improvements that will also lead to timelier patient access to safe and effective devices.

Of course, there are many areas where FDA could further enhance the predictability and efficiency of its review process, and the new MDUFA IV agreement lays the groundwork for further FDA performance improvements through more ambitious goals, important process changes, and increased accountability, supported by additional resources.

This agreement is good for industry. It is good for FDA. Most of all, it is good for patients. We urge this committee and the Congress as a whole to act promptly to reauthorize the user fee program and enact this agreement into law. Failure to act would not only jeopardize the critical improvements made by the new agreement but would have a devastating impact on our industry's ability to bring innovative diagnostics, treatments and cures to patients.

The user fee agreement builds the conditions for success in a number of major ways.

*Significant Improvements for Total Review Time Goals*

Measuring the total time from submission to an FDA decision to either make that technology available to patients or deny approval is the most meaningful measure of the process. Total time goals were first included in MDUFA 5 years ago, and have been a meaningful measure for both industry and FDA. Building on the total time goal, this MDUFA IV agreement will continue to drive toward reducing the total time that is spent reviewing a submission.

The MDUFA IV goals for total time reviewing a product represent substantial improvements over current performance. For 510(k) products, which are moderate-risk medical devices, the total time goal is currently 124 days. The MDUFA IV agreement lowers that goal to 108 days by the fifth year. This represents a 13 percent decrease, which returns the total time to historical norms.

For PMA products, which are the most innovative and highest risk products, the total time to decision goal is currently 385 days. The MDUFA IV agreement lowers that goal to 290 days by the fifth year. This represents a 25 percent decrease.

For the first time, the MDUFA IV agreement includes goals for *de novo* products, which are generally moderate risk products but brand new innovations, which FDA has never evaluated before.

*Patient Input and Involvement in the Regulatory Process*

As we all know, patients have a critical voice in product development and evaluation. This MDUFA IV agreement will have increased resources dedicated to supporting patient involvement in the medical device regulatory process. FDA's device center has taken several steps to incorporate the patient perspective into the device review process, through efforts such as voluntary patient preference information and voluntary patient reported outcomes, and this agreement will continue to support that work.

*Process Improvements*

Third, the agreement includes process improvements that we anticipate will enhance the consistency and timeliness of the review process, independent of the specific time goals.

One such example is that the agreement provides for meaningful presubmission interactions between FDA and companies. Interactions between the sponsor of a medical device application and the FDA, prior to the formal submission of a product application, can provide helpful guidance that aids the sponsor in ensuring their application contains all necessary information. This presubmission process was first put into place 5 years ago, in MDUFA III, and has benefited both industry and the FDA. This MDUFA IV agreement builds upon this success by adding in a specific time commitment tied to pre-submission meetings. Under the MDUFA IV agreement, FDA will be required to provide meaningful, written feedback to companies at least 5 days prior to a presubmission meeting, ensuring that the meeting will be a productive one.

Additionally, the agreement supports FDA's efforts to establish a National Evaluation System for Health Technologies, or the NEST. MDUFA funding will be used

for a pilot to assess whether real-world evidence can be used to support premarket activities. This NEST pilot will determine the usability of real-world evidence for expanded indications for use, new clearances and approvals, and improved adverse event reporting.

*Greater Accountability*

Fourth, the agreement provides for greater accountability. Greater accountability means that FDA's success under this agreement will be transparent to FDA management, to industry, to patients, and to Congress and the Administration, so that any problems that arise can be corrected promptly. New reporting tools and two independent management reports will provide key data to track FDA performance, highlight any failures to meet key goals, and provide the basis for corrective actions.

One of these critical accountability measures involves process reforms for deficiency letters, or letters that applicants receive when their submission is found by FDA to be lacking needed information. Under this MDUFA IV agreement, all deficiency letters will include a statement of what information was provided in a submission and why it is not sufficient, including specific reference to the basis for the deficiency determination. Additionally, all deficiencies will undergo supervisory review by management prior to being issued. These provisions ensure that deficiency letters focus on real data needs and that FDA is clear on what data they require.

In addition, the agreement provides for two analyses of FDA's management of the device review process. This review, or independent assessment, was a critical part of the MDUFA III agreement that helped lead to improvements in FDA performance. The MDUFA IV agreement continues this success by including funds for two additional independent reviews, one at the beginning of MDUFA IV and one at the end.

*Enhanced Resources*

Finally, to give FDA additional tools to meet the new goals, the agreement provides $999.5 million (fiscal year 2015 dollars) in user fees for 2018–22. This is built off of a baseline of approximately $679 million from MDUFA III, along with an additional $228 million in new resources to improve the device review process. In addition, there are $92.5 million in onetime costs for items such as IT and infrastructure improvements. Collectively, the resources will give FDA what it needs to continue to improve performance.

Each of the provisions of this agreement has the potential to make a difference in continuing to improve FDA performance. But the whole is truly greater than the sum of its parts. Each of the elements of the agreement reinforces the others.

Of course, no agreement, no matter how good on paper, is self-executing. Making it work as intended will require the full efforts of FDA's dedicated staff and managers. Our industry is committed to working with FDA in any way we can to make it a success. Continued oversight and interest from the Congress will also be important. Patients are depending on all of us.

## CONCLUSION

Finally, I should note that we are appreciative of efforts by all Members who seek to give the FDA the tools and structure it needs to succeed. Legislative reforms that do not alter the substance of the negotiated agreement between FDA and industry hold the potential to create a legislative reauthorization package that maximizes the opportunity for success at the agency, which should be the shared goal of all involved.

For example, legislation has been proposed to improve the consistency and transparency of FDA inspections of medical device facilities and to move to a risk-based system for device inspections. These common-sense proposals will ensure that FDA's inspections resources are best targeted to public health needs and that companies and FDA are working together.

I appreciate the committee's work in considering these and other appropriate measures that enhance and compliment the underlying user fee agreement, and its focus on enactment of this legislative package as soon as possible.

To reiterate, the MDUFA IV agreement is good for industry. It is good for FDA. Most of all, it is good for patients. We strongly support the vital improvements made by the new agreement and believe that a failure to act would have a destructive impact on our industry's ability to bring new, innovative treatments and cures to patients.

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

The CHAIRMAN. Thank you, Mr. Whitaker.
Ms. Bens.

**STATEMENT OF CYNTHIA BENS, VICE PRESIDENT OF PUBLIC POLICY, ALLIANCE FOR AGING RESEARCH, WASHINGTON, DC**

Ms. BENS. Chairman Alexander, Ranking Member Murray, and distinguished members of the committee, it's really an honor for me to be here to speak to you about the prescription drug and medical device user fee programs.

Right now, approximately 10 percent of the U.S. population is over the age of 80. This 80-plus age group will reach 30 percent of the population by the middle of the century. Many older adults today are fortunate to experience better health as they age than previous generations.

The truth is that most older adults still face significant periods of illness and disability later in their life. They develop one or more forms of cardiovascular disease, cancer, diabetes, bone and joint degeneration, muscle wasting, vision and hearing loss, neurological diseases, and incontinence.

In our view, the need for innovative treatments and medical devices that respond to the physical declines people face with age has never been greater. We believe we will only realize the benefits of innovations if the FDA has access to the resources and expertise necessary to evaluate them, industry is certain that their products are going to be assessed in a timely manner, and patients are at the center of new product development.

The PDUFA VI and MDUFA IV agreements contain critical commitments and funding for the FDA that will benefit patients. The agreements do this by strengthening the agency's workforce, expanding patient-focused clinical development activities, improving FDA's capacity to advance the use of innovative clinical trial designs, and harnessing the potential of real-world evidence in regulatory decisionmaking.

Without the necessary number and types of staff, the agency will not be able to reduce product review times and meet other ambitious performance goals for which the PDUFA VI and MDUFA IV resources are intended. The user fee agreements increase the number of staff dedicated to drug and device reviews and put much-needed resources into hiring and retention practices at the FDA.

PDUFA V and MDUFA III laid a solid foundation for FDA to incorporate patient perspectives on the benefits and risks of medial products and their hopes for successful treatment into the regulatory process. PDUFA VI and MDUFA IV build on this foundation by allowing the FDA to add staff with clinical, statistical, psychometric, and health outcome skills. This staff will enhance FDA's capacity to guide the incorporation of patient-reported outcomes and other patient-focused measures into drug or device development.

To complement the internal changes at the FDA, the PDUFA VI and MDUFA IV agreements lay out a clear process for building external capacity to develop patient-centered measures and gather patient-preference information. They do this through hosting several public meetings and developing guidance that will include patients, patient advocates, researchers, and industry.

To advance innovation in clinical trials, the PDUFA VI agreement details an early consultation process between FDA senior leadership and industry on the use of new surrogate endpoints. The meetings will identify knowledge gaps that require attention and provide insights on the feasibility of using a surrogate as the basis for an approval.

Currently, these conversations happen too late in the clinical trial process, and companies don't have the ability to change course. It can be costly, it can lead to discontinuation of trials, and trial failures, and patients are really the ones that suffer when these products don't make it through.

PDUFA VI also greatly enhances FDA's ability to advance the future of drug development. In particular, the PDUFA VI agreement addresses model-informed drug development and complex design issues by providing the agency with additional staff and funding for meetings to guide FDA and industry's incorporation of innovative clinical trial methods.

Modeling and simulations important to the early development of combination treatments for diseases such as Alzheimer's disease and adaptive clinical trials for employing advanced statistical methods are essential when you're testing these multidrug regimens. We're optimistic that combination therapy will be a successful part of Alzheimer's treatment in the future, and we believe that the PDUFA VI resources can help FDA work with industry and the patient community to make this a reality.

The PDUFA VI and MDUFA IV agreements expand the use of real-world evidence to deepen our understanding of how products are working, to support the incremental progress of clinical development, and lead to optimal care. Older adults are often excluded from clinical studies because of their advanced age or the presence of co-morbidities, even though they may be the majority of users of these products.

Data on medical products generated as part of the practice of medicine has really been critical in understanding how new treatments and devices are functioning in this population. MDUFA IV will establish a coordinating center for the National Evaluation System for Health Technology. The NEST coordinating committee will undertake pilot programs to explore the usability of real-world evidence for determining expanded indications and new device approvals as well as device malfunction reporting.

In the future, we believe this system has the potential to decrease the number of standalone trials, increase enrollment efficiencies, and make patient follow-up less burdensome, and we look to the future of a time when more active surveillance of safety issues can be a part of NEST. PDUFA VI goes beyond the current use of real-world evidence for assessing post-market safety and will allow FDA the ability to explore the use of this valuation information in assessing a product's efficacy.

The PDUFA VI and MDUFA IV agreements will increase the efficiency of the regulatory process, reduce the time it takes to bring safe and effective medical products to market, and, most importantly, it puts patients at the heart of new product development. I'll close by reiterating our strong support for the successful reauthorization of these programs.

Thank you for the opportunity to present our views today.
[The prepared statement of Ms. Bens follows:]

PREPARED STATEMENT OF CYNTHIA BENS

SUMMARY

The Alliance for Aging Research is the leading non-profit organization dedicated to accelerating the pace of scientific discoveries and their application to improve the experience of aging and health.

The Alliance participated in monthly patient/consumer stakeholder consultations with the FDA leading up to the release of negotiated agreements for PDUFA VI and MDUFA IV. The Alliance for Aging Research strongly supports these agreements.

The U.S. population is aging rapidly and most older adults face significant periods of illness and disability later in life. For this reason, the need for innovative treatments and medical devices that respond to declines people face with age has never been greater. To foster innovation, FDA requires additional resources and expertise, drug and device reviews must be accelerated, and patients should at the center of product development address their most pressing needs.

The Alliance believes that the PDUFA VI and MDUFA IV agreements will strengthen the agency's workforce to speed up review times, expand patient-focused medical products development activities, improve FDA's capacity to advance the use of innovative clinical trial designs, and harness the potential of real-world evidence in regulatory process.

The Alliance urges timely reauthorization of the PDUFA and MDUFA programs because of the critical funding they provide for the FDA and commitments the agreements contain that will benefit patients.

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Chairman Alexander, Ranking Member Murray, and Distinguished Members of the committee: It is an honor and a privilege to speak with you today on behalf of the Alliance for Aging Research, about the reauthorization of the Food and Drug Administration's Prescription Drug User Fee Act (PDUFA) and Medical Device User Fee Act (MDUFA) programs.

I am Cynthia Bens, vice president of public policy at the Alliance. The Alliance for Aging Research is the leading non-profit organization dedicated to accelerating the pace of scientific discoveries and their application to improve the experience of aging and health. We believe that advances in research help people live longer, happier, more productive lives and reduce health care costs over the long term.

Most of us are keenly aware that our population is aging at an unprecedented rate. Ten thousand Baby Boomers are turning 65 each day. This is up from 6,000 per day just 6 years ago. People age 85 and older are the fastest growing segments of our population. Right now, approximately 10 percent of the U.S. population is age 80 or older. This 80+ age group will reach 30 percent of the U.S. population by 2050.

Many older adults today are fortunate to experience better health as they age than previous generations. The truth is that most older adults still face significant periods of illness and disability later in life, often from multiple chronic conditions that require complex care management. They develop one or more forms of cardiovascular disease, cancer, diabetes, bone and joint degeneration, muscle wasting, vision and hearing loss, neurological diseases, and incontinence.

In our view, the need for innovative treatments and medical devices that help respond to the physical declines people face with age has never been greater. We believe that we will only realize the benefits of these innovations if the FDA has access to the resources and expertise necessary to evaluate them, industry is certain that their products will be assessed in a timely manner, and patients are at the center of new product development.

For more than a decade, the Alliance for Aging Research has worked directly with the FDA, other patient advocates, researchers, and industry on ways to streamline the regulatory process for the benefit of older adults. We understand that user fees play an essential role in maintaining FDA review processes that efficiently deliver safe and effective medical products to patients who need them, and that is why we engage in the prescription drug and medical device user fee reauthorization processes.

HISTORICAL PERSPECTIVE ON THE PDUFA AND MDUFA PROGRAMS

Prior to the last reauthorization of PDUFA and MDUFA, patient organizations were not allowed to engage in the negotiations between the FDA and industry. Thanks to your committee's leadership and the support of your colleagues in Con-

gress, the Alliance for Aging Research and other groups were represented throughout the patient/consumer stakeholder consultation phase leading up to PDUFA V and MDUFA III. We had an opportunity to provide feedback to the FDA as negotiations were taking place and propose enhancements to be included in the final commitment letter that emerged from the negotiations.

Engagement from the all stakeholders during the PDUFA V and MDUFA III negotiations resulted in final agreements that provided resources to strengthen review capacity at the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH); advance regulatory science activities across medical product divisions within the FDA; and begin a movement toward more patient-centered medical product development, both inside and outside of the agency.

The Alliance for Aging Research was honored to offer patient perspectives to CDER and CRDH through monthly stakeholder consultations and public meetings held over the last year as the agency negotiated the PDUFA VI and MDUFA IV agreements. PDUFA VI and MDUFA IV contain critical commitments and funding for the FDA that we strongly support.

We are thankful the reauthorization of the user fee agreements is a priority for this committee, and that patient benefit maintains a central role. We call your attention to the following sections of the agreements that provide additional resources for CDER and CDRH's workforce, expand patient-focused medical products development activities, improve FDA's capacity to advance the use of innovative clinical trial designs, and harness the potential of real-world evidence in regulatory decisionmaking. These provisions will enhance FDA's ability to evaluate safe and effective treatments in a manner that will be meaningful to patients.

PDUFA VI AGREEMENT BENEFITS TO PATIENTS

*I. Strengthening CDER's Workforce*

The FDA lacks several tools that would allow it to maintain a robust hiring and retention function, which is why the Alliance for Aging Research pushed for a focus on hiring during PDUFA VI, and during the development of the 21st Century Cures Act. The 21st Century Cures Act took some positive steps to loosen restrictions on hiring for high-level vacancies but we are pleased to see that industry is putting resources toward more general hiring and retention processes at FDA in the PDUFA VI agreement. There are several proposed enhancements under Section III of the PDUFA VI agreement to ensure CDER's workforce stability and establish first-ever goals for hiring.

Section III of the PDUFA VI agreement improves CDER's hiring and staff retention practices. This is one of the most critical components of the agreement because the agency will only be successful if it has the best and the brightest people in its' workforce. To do this, CDER needs to compete on a level playing field with the private sector and other Federal agencies for highly skilled individuals.

Section III–A. of the PDUFA VI agreement modernizes CDER's hiring system. Two highlights of this section are: (1) a commitment to implement a comprehensive online position classification system and (2) a transition away from time-limited individual position vacancy announcements. Shifting to common vacancy announcements—to be used by multiple offices for continuous posting—will provide the greatest opportunity for applicants with key scientific and technical expertise to apply for positions regularly needed across FDA's drug review programs.

Section III–C. of the agreement establishes a dedicated unit with a continuous focus on hiring and staffing. This unit will help CDER keep pace with scientific and technologic advances by proactively reaching out to qualified candidates and competitively recruiting to fill vacancies. It will analyze compensation and other factors that affect retention of key staff on an annual basis. The PDUFA VI agreement also allows the agency to retain a qualified hiring contractor to augment CDER's existing hiring staff capacity. Employing this contractor will assist FDA in successfully meeting goals for recruitment of human drug review program staff.

CDER was required to implement the Breakthrough Therapy Pathway during PDUFA V. This pathway was intended for new drugs that showed exceptional promise for effectively treating a disease or patient population with an unmet need. This Breakthrough Pathway has been more successful than was intended and resulted in patients having quicker access to truly innovative products for serious and life-threatening conditions. Unfortunately, this pathway has placed a strain on the agency because it is resource-intensive and did not come with additional funding under PDUFA V. PDUFA VI provides the addition of more than 30 staff to assist with this expedited pathway, which will help streamline approvals and ensure pathway integrity.

PDUFA VI also makes critical changes to the FDA's communications with sponsors that will help expedite drug development. CDER will maintain dedicated staff to provide communications training to their medical product review divisions, to better facilitate responses to general questions from sponsors and ensure timely resolution of issues with specific new drug applications. PDUF VI fees will support an independent assessment of current communications practices and a public workshop to examine the results of this assessment.

*II. Expanding Patient-Focused Drug Development*

The Alliance for Aging Research has been a strong advocate for the Patient-Focused Drug Development (PFDD) Initiative since the PDUFA V negotiations. At the urging of our Aging in Motion (AIM) coalition, a disease of aging called sarcopenia was selected for an FDA-led PFFD meeting. The meeting will be held later this week. The 27 PFDD meetings held by FDA on select diseases are providing FDA medical reviewers with a fuller understanding of patient and caregiver experiences with a disease and their hopes for successful treatment. The Alliance supported the continuation of FDA-led PFDD meetings as part of PDUFA VI and we are pleased that FDA will have the flexibility under Section J of the agreement to utilize user fee funds for disease-specific meetings, if they determine them to be useful.

PDUFA VI will add staff with expertise in patient-focused methods to be embedded into the review divisions. It is anticipated that these individuals will provide clinical, statistical, psychometric and health outcomes skills to enhance FDA's capacity and guide the incorporation of patient-reported outcomes and other patient-focused measures into drug development programs.

To compliment the internal changes at FDA in PFDD, the PDUFA VI agreement lays out a clear process for developing sequential guidance, with full participation from the patient advocacy community, industry and FDA on the collection of patient input leading to the development of patient-centered measures. We strongly support FDA's leadership in PFDD, because there is no one patient advocacy organization or company that can or should speak for all patients, and because the process is ultimately meant to inform improved medical product development within FDA's review divisions. The proposed public process in PDUFA VI maintains and clarifies FDA's role, while providing much-needed user fee funding for external capacity building. To help ensure that there is efficient use of patient group and industry resources when pursing the development of novel patient-focused drug development tools, CDER will create and maintain a repository of existing clinical outcome assessments, patient-focused meeting resources, and other patient-focused efforts.

Since PDUFA V, we have supported the dedication of user fees to develop a transparent and structured benefit-risk framework for drug evaluation. Understanding the components of FDA's benefit-risk assessment and how these components are applied in the context of regulatory decisionmaking continues to be of keen interest to industry and the patient advocacy community. PDUFA VI updates CDER's benefit-risk implementation plan, calls for a public meeting and the addition of a draft guidance to enable more productive activities that capture patient experiences, and allows for the communication of those findings to CDER throughout the drug development process.

*III. Advancing Innovative Clinical Trials*

In 2012 and 2013 the Alliance convened two impactful meetings on combination therapy development for Alzheimer's disease. These meetings highlighted that modeling and simulation will be important in the early development of drug-drug combinations and that adaptive clinical trials employing advanced statistical methods will be essential in testing any multi-drug regimen for Alzheimer's disease. We are optimistic that combination therapy will be a successful part of Alzheimer's disease treatment in the future. PDUFA VI greatly enhances CDER's ability to advance the future of drug development through the addition of staff with expertise in statistical modeling and innovative clinical trial designs. Section J of the PDUFA VI agreement addresses model-informed drug development and complex design review by providing CDER with additional staff and funding for public meetings to guide FDA's and industry's incorporation of innovative clinical trial methods.

The Alliance for Aging Research has first-hand experience with the FDA's Drug Development Tool (DDT) Qualification Process. We participated in efforts to qualify multiple tools for use in clinical trials for Alzheimer's disease and we are currently pursuing qualification of two functional assessments to be used as endpoints in clinical trials for sarcopenic patients. We feel strongly that the DDT Qualification Process should continue because it provides a unique space for collaboration and resource pooling among multiple stakeholders, including patients, to advance patient-centered endpoints that are made available in the public domain. PDUFA VI ex-

pands base capacity within the qualification review team and provides them with funding to host a series of meetings resulting in guidance that will strengthen the DDT Qualification Process.

The PDUFA VI agreement also details a process for early consultation with drug sponsors on the use of new surrogate endpoints in clinical trials. The meetings described in the agreement will allow companies to engage with FDA's senior leadership on the feasibility of using a surrogate endpoint that has not previously been used as the basis for an approval. Meetings like these will identify any knowledge gaps that require attention. While we do not yet have qualified biomarkers for use as surrogates to test drugs for many diseases of aging, we know that clinical trials utilizing surrogate endpoints will be increasingly important as drug development moves toward early intervention and prevention of age-related diseases. Establishing this dedicated process for meetings on surrogates between FDA and industry that can occur as early as end of Phase 1, is a priority for us.

*IV. Harnessing the Potential of Real-World Evidence*

The PDUFA VI agreement enhanced the use of real-world evidence in regulatory decisionmaking. Data on medical products generated as part of the practice of medicine is already being successfully utilized for the purposes of assessing a product's safety in populations that are underrepresented in randomized controlled trials (RCTs). Older adults are often excluded from RCTs due to advanced age or presence of comorbidities, even though they are often most of the users for a given intervention. Real-world evidence has been critical in understanding how new treatments are performing in this population when they enter the post-market space. We support FDA's efforts under PDUFA VI to go beyond the current use of real-world evidence for assessing safety post-market and to explore how this valuable information can be used in assessing a product's efficacy. PDUFA VI fees will support multi-stakeholder public workshops, methodology-development pilot programs and regulatory guidance. We believe that this represents a sound, comprehensive approach to harnessing the potential of real-world evidence for patients, product sponsors, and the agency.

MDUFA IV AGREEMENT BENEFITS TO PATIENTS

*I. Supporting CDRH's Workforce*

Having expert CDRH staff to carry out user-fee-funded activities is paramount. Without the necessary number and types of staff, CDRH will not be able to meet the ambitious performance goals for which the MDUFA IV resources are intended. MDUFA IV provides CDRH with needed funding to hire across medical device review activities and cultivate existing staff. Specifically, Section III–B of the MDUFA IV agreement permits CDRH to apply user fees for the improvement of its scientific and regulatory review capacity. With these fees, CDRH intends to increase the retention rate of high-performing supervisors, reduce the ratio of review staff to supervisors, hire new device application reviewers, and utilize recruitment support to augment existing human resource services.

The Alliance for Aging Research is supportive of Section IV–E of the MDUFA IV agreement that seeks to bolster the third-party review program within CDRH. We advocated for the use of MDUFA III fees for the third-party review program so that CDRH's staff would have more time to devote to higher-risk device applications. It is our understanding that third-party review continues to be valuable for lower risk devices, but the program requires improvements to make it more efficient. We are glad that CDRH continues to have the resources and flexibility to employ outside experts as needed under MDUFA IV and that there will be improvements made to the third-party review program to ensure its integrity.

MDUFA IV will lead to significant reductions in the time it takes the FDA to review the most common types of medical device applications. This will not only benefit industry, but also accelerate patient access. Under MDUFA IV, the FDA has committed to reduce the days for review of 510(k) applications and for premarket approval (PMA) applications. FDA also set goals for reviewing *de novo* applications. The number of *de novo* requests has increased steadily since the pathway was created. The limited resources currently available to the agency for *de novo* requests have resulted in missed target dates for review in all but 40 percent of cases. Section II–E of the MDUFA IV agreement specifies that the agency set a goal of reviewing 70 percent of *de novo* requests on time by fiscal year 2020.

*II. Expanding Patient-Centered Medical Device Development*

The Alliance for Aging Research applauds the FDA for fostering the use of patient preference information in the review and approval of medical devices. CDRH was a leader among regulators in aggressively pursuing a transparent and structured

benefit-risk framework. Finalizing a benefit-risk guidance for devices was one of CDRH's first actions in MDUFA III implementation. The benefit-risk guidance, first issued by FDA in 2015, broadly defines the benefits they are interested in understanding. The type of benefit CDRH specifically calls out are not just a device's impact on clinical management of a disease and patient health, but also patient satisfaction, improvement in quality of life, improvement in function, reduction in lost function, reduction in probable mortality, and symptom relief. For diagnostics, benefit could be assessed on public health impact, the ability to identify a specific disease and potentially prevent its spread, predicting future disease onset, providing earlier diagnosis of diseases, or identifying patients more likely to respond to a given therapy.

The benefit-risk guidance also laid out the ways in which CDRH assesses the magnitude of benefit, the probability of a patient experiencing benefit, and the duration of benefit. The guidance provides details, some examples, and a copy of the worksheet that reviewers use in their benefit-risk determinations.

Benefit-risk calculation is discussed frequently but there is the potential for this type of exercise to be more tokenism than substance. CDRH got the substance of the patient experience right, and that is because they actively engaged with the patient advocacy community to best characterize disease severity and unmet need from the start.

Of late, industry has begun including patient-centered endpoints in development programs, signaling a growing interest by industry to employ patient-reported outcomes in device trials with more regularity. FDA has responded by drawing patient representatives earlier into the device review process, developing a systematic benefit-risk framework for the evaluation of new devices, and creating a Patient Engagement Advisory Committee.

Section IV–F of the MDUFA IV agreement details activities that CDRH will take to further advance patient input and involvement in the regulatory process. CDRH will develop scientific expertise and expand staff capacity to respond to device submissions containing publicly available, and validated, patient preference information or patient-reported outcomes. This section also calls for public meetings to discuss approaches for incorporating patient-preference information and patient-reported outcomes as evidence in device submissions, as well as other methods of advancing patient engagement. CDRH will also explore ways to use patient input to inform clinical study design and reduce barriers to patient participation by facilitating recruitment and retention. The MDUFA IV agreement calls on the FDA to identify priority areas in which patient preference information could inform regulatory decisionmaking and requires publication of these priorities in the *Federal Register*.

*III. Utilizing Real-World Evidence*

The Alliance sought the application of MDUFA IV resources to elevate CDRH's ability to further real-world evidence generation for the purposes of informing regulatory activities. We believe that the collection of data generated through routine clinical care can help broaden our understanding of how products are working in the real world, support the incremental process of medical device development, and lead to optimal care.

Under Section IV–H of the MDUFA IV agreement, CDRH can utilize user fees to hire staff with expertise in the use of real-world evidence and establish a coordinating center for the National Evaluation System for health Technology (NEST). NEST will link health claims, electronic records, and registry data. In the future, these activities have the potential to decrease the number of stand-alone clinical trials, increase enrollment efficiencies, and make patient followup less burdensome.

With MDUFA IV funds, the NEST Coordinating Committee will undertake a pilot program to explore the usability of real-world evidence for determining expanded indications for device use, new device approval, and device malfunction reporting. The NEST pilot program is particularly meaningful for our organization since older adults are not adequately represented in many clinical studies for devices.

The Alliance for Aging Research requests one change to the MDUFA IV agreement. Section IV–H states that, "Industry representation on the NEST governing board will make up at least 25 percent of the governing board membership." MDUFA IV generally references anticipated representation of the patient community on the NEST governing board. We believe that the enacting legislation should detail the composition of the remaining 75 percent of the governing board and include representatives of patient populations most likely to be affected by increased utilization of real-world evidence (e.g., the elderly, those with multiple chronic conditions, women, etc.). If patient preference is truly a priority for the FDA and industry, representation by patient representatives on the NEST governing board should be more clearly outlined.

CONCLUSION

As mentioned previously, the Alliance for Aging Research strongly supports the continuation of the prescription drug and medical device user fee programs through the negotiated PDUFA VI and MDUFA IV agreements. The Alliance advocates for increased overall funding of the FDA, with strong emphasis on finding the right balance between user fees and appropriated funding. We think that the size and scope of the proposed fees within the PDUFA VI and MDUFA IV agreements is appropriate and necessary to increase the efficiency of regulatory processes, reduce the time it takes to bring safe and effective medical products to market, and put patients at the heart of new product development.

Despite the opportunities afforded by PDUFA VI and MDUFA IV, we are all in jeopardy if the FDA's budget authority remains flat or is significantly reduced in the coming fiscal year. As you are aware, not all FDA activities can be supported through user fees, nor should they be. Crucial safety and surveillance activities as well as oversight of over-the-counter medications and other products, currently fall outside of the user fee programs. While FDA appropriations are not under the jurisdiction of this committee, it is our hope that you will join us in calling for sufficient budget authority to maintain the overall health of this essential agency.

Thank you for the opportunity to present our views today. The Alliance for Aging Research is grateful that the committee is making the reauthorization of the user fee programs a priority and we look forward to working with you on enacting legislation for these important programs.

I am happy to answer any questions you may have.

The CHAIRMAN. Thank you, Ms. Bens, and thanks to all of you. We'll now have a 5-minute round of questions, and I'll defer mine and go first to Senator Scott.

## STATEMENT OF SENATOR SCOTT

Senator SCOTT. Thank you, Mr. Chairman.

Good morning to the panel. Thank you all for being here this morning.

We've talked a lot about patient-centered healthcare delivery. It makes sense that in the drug development space, we want to make sure that there's room for patients' voices as well. I applaud the commitment to patient-focused drug development in PDUFA V. I was glad to see that 1 of the 20 meetings held with the public focused on the sickle cell disease and having the input from the patients as well as the caregivers in this space.

Their stories are very important for a number of reasons. They teach us about the disease and how it devastates not only the person but the family. They teach us a lot about the resiliency of kids and how they're able to maintain a positive attitude through hospitalization after hospitalization, after visits to the emergency room, so things that are a very important part of the conversation.

Ms. Holcombe, what do you think the industry learned and could continue to learn from this type of patient input, and how can that shape in a tangible way the drug development process?

Ms. HOLCOMBE. Thank you, Senator, for that question. There is an important step that PDUFA VI will be taking that builds on all of the learnings of those meetings with patient organizations. One of the things that researchers learned and that FDA learned from those patients and those patient advocates was that sometimes the way we see their condition is not the way they see their condition.

So the question really is, if we're developing a therapy for someone, shouldn't we try to understand as well as we can what the person needs and what that person wants? What are the symptoms that bother those patients most? What are the things that deter them from participating in clinical trials? Why don't they sign up

for trials? Why don't they stay in trials when they get in trials to test new drugs?

Learning those kinds of things, learning how to convert those compelling narratives from those patients into real data that can be used in the approval of a product, in the design of a trial, that will actually measure what is important to those patients will be a huge step forward in developing drugs that completely have the patient at the center of the concept.

Senator SCOTT. Thank you for your answer. I will say that I know that in many ways, the African American community does not necessarily participate at high rates in drug testing. Your comments lend themselves to having more folks participate in that process as they understand and appreciate the necessity of it and as industry does exactly the same as well. Thank you for your answer.

Startups have played a big role in bringing new and innovative therapies to market. These small companies are doing inspiring work and are dedicated to improving patients' lives more often than not with a really bare bone staff. I hope that we will continue to create an environment in our country where these startups can thrive, because they are, in fact, a part of what sets us apart.

Once again, Ms. Holcombe, your organization represents a lot of these small companies. How important was the enhanced communication program established in PDUFA V for these smaller companies, and how will PDUFA VI build on this to give them the support they need?

Ms. HOLCOMBE. Well, the enhanced communication program was critical for these companies, because they are on kind of a short string, if you will. They have a limited amount of time and a limited amount of resources, and when they get hung up on some small but technically important question, they need to be able to get an answer quickly. Waiting for the process, even though it's a pretty efficient process, of an FDA formal meeting is just not feasible for them.

The informal communications system allowed them to reach out to FDA on a less formal basis and get an answer that will allow them to proceed with their development program in a timely way. Those processes will continue under PDUFA VI, and, in addition, a third-party evaluator will come into the agency and look at how these processes are playing out across all of the review divisions and see whether there are best practices that make some of the divisions more responsive than others and try to then identify those best practices and disseminate them across the entire center.

Senator SCOTT. Thank you, ma'am.

Mr. Chairman, I'm out of time.

The CHAIRMAN. Thank you, Senator Scott.

Senator Murray.

Senator MURRAY. Thank you very much. I hear from patients and families and doctors and hospitals and businesses in my home State of Washington all the time about the astronomical cost of drugs. Our work here today, obviously, on this committee is to advance the FDA user fee agreement to help support a robust and competitive market for safe and efficient drugs.

We've got to do more to reign in costs. We're often told that families here in the United States pay more than citizens of other western countries for the same drugs because manufacturers need the high returns to invest in research and development, and I strongly support policies that promote investment in research and development. That's why I was proud to work with Senator Alexander and many of our colleagues here today on the 21st Century Cures Act.

I'm concerned because a recent analysis by researchers at Sloan Kettering suggests the high price Americans pay for their prescriptions is far more than these companies need to cover the cost of their entire global R and D budgets. Given those findings, my question is simple.

Ms. Holcombe, I'm going to ask you. Why can't drug companies just provide more transparency into how they set their prices?

Ms. HOLCOMBE. Thank you, Senator Murray. I don't exactly know how to answer that question, obviously. The problems that families face in our country of the high cost of healthcare, in general, are problems that we all need to work together to solve. Understanding how drug prices are set and what they end up being is complicated. Whether we can improve the transparency is something that we certainly, at BIO, would be very happy to look at in depth with you and talk about how this kind of thing could happen.

It's important to realize that the price that a patient is paying at the pharmacy counter, for example, is not the price that is set by a drug company, but it is the price that the insurance plan that this individual has is allowing to happen. It's a system in which there are many players. We have to figure out together how to make that system work better for American families, and we at BIO, who represent companies that make important medications, as you point out, are very open to working with all the other members of that system, insurance companies, PBMs, and so forth, to figure out how we can do things better for American families.

Senator MURRAY. Well, transparency is an important part of that, and I want to talk to you about that, on ways that we can improve that.

During the development of 21st Century Cures, my fellow Democrats and I supported an amendment to improve post-market surveillance of medical devices so we could better understand their safety and their effectiveness.

Ms. Bens, let me talk to you. While that amendment was not adopted, can you tell us briefly how much surveillance could have a positive impact on older Americans, many of whom count on medical devices both in the doctor's office and at home?

Ms. BENS. Sure, absolutely. Thank you so much, Senator Murray, for that question.

The FDA currently has the authority to issue two types of post-market studies. One is a post-market study that's conducted and decided on by the manufacturers at the point of product approval, and then the second type of study usually comes about once a product is on the market, and there is determined to be some sort of safety signal.

The GAO actually released a report in 2015 that was looking at the progress that FDA was making in enforcing some of those post-market studies, both on the full post-market studies as well as

post-market surveillance, and they found that at the time, most of those studies were making adequate progress. One of the major problems with the ones that weren't making progress was largely due to the fact that they were having trouble enrolling enough study participants to participate in those trials, and so it was delaying them.

One of the things that we're supportive of is the establishment of NEST. The reason that we think it's really important is it is going to keep building on this infrastructure of making sure that there is linking between the electronic health records data and other types of claims, where you can be studying these products once they go onto the market for longer periods of time. Typical post-market studies have a 3-year window, and we think that NEST will be able to provide in the future much more real-time assessments.

Senator MURRAY. All right. I'm almost out of time.

Mr. Whitaker, I want to ask you, because I'm really disappointed that the medical device industry has explicitly refused to fund its user fees to assess the safety of medical devices already on the market. The drug industry has supported FDA's post-market surveillance activities with user fees since, actually, 2007. Why does the device industry refuse to follow that lead?

Mr. WHITAKER. I don't believe, Senator Murray, we're opposed to post-market surveillance activity. The focus of this user fee agreement from the beginning was just on pre-market activities. We did not engage in a conversation with FDA about expanding it beyond its original remit. All of our conversation about MDUFA IV was reauthorizing the current agreement and increasing resources to help support FDA to meet the current goals that they had set. We didn't go beyond that in the scope of our internal conversations with them.

Senator MURRAY. Mr. Chairman, let me just say that the issue of duodenoscopes medical devices in my home State of Washington led to a horrible situation, and I think the industry can do more to support medical device safety for consumers. And just as a note, 2 weeks ago, another outbreak of antibiotic resistant infections was traced back to the same devices that the company said were fixed after that outbreak in Washington, and I really believe we need to support more action and I want to work with you on that.

The CHAIRMAN. Thank you, Senator Murray.

Senator Burr.

## STATEMENT OF SENATOR BURR

Senator BURR. Thank you, Mr. Chairman.

My first two questions are to Mr. Whitaker, Mr. Gaugh and Ms. Holcombe, and it's a yes or no question. In the past 4 years, in the current years of the user fee agreement, has the FDA met 100 percent of their negotiated deliverables?

Mr. Whitaker.

Mr. WHITAKER. I don't know the number. I don't know that it's 100 percent, but they've made tremendous progress.

Senator BURR. Mr. Gaugh.

Mr. GAUGH. I would have to say they have hit 100 percent of their negotiated metrics.

Senator BURR. Ms. Holcombe.

Ms. HOLCOMBE. Yes. Under PDUFA, they have met 100 percent of their goals.

Senator BURR. Would your industry be supportive of this committee requiring that FDA report to us specifics on their deliverables on a timeline on a regular basis?

Mr. Whitaker.

Mr. WHITAKER. As a part of their reporting requirements, that seems reasonable to us.

Senator BURR. Mr. Gaugh.

Mr. GAUGH. Yes.

Senator BURR. Ms. Holcombe.

Ms. HOLCOMBE. Yes.

Senator BURR. Ms. Holcombe, how significantly different is what you negotiated both last time and in this one reflective of differences between the FDAMA 1997 statutory language?

Ms. HOLCOMBE. FDAMA was visionary, and this PDUFA VI agreement is keeping that vision in mind to transform the drug development process.

Senator BURR. If FDA followed the statute of the law, would you have to negotiate this?

Ms. HOLCOMBE. I still think that FDA requires additional resources to carry out some of these activities.

Senator BURR. FDAMA covered specifics about communication and timelines.

Mr. Whitaker, let me go to you, because I'm going to go to your own testimony. You said MDUFA IV will reduce review times on 510(k) to historical norms. Explain to me why the device industry should pay $320 million increase in user fees to get back to your historical norms.

Mr. WHITAKER. Well, we think anything we can do to reduce the timelines to decision is important, and getting back to what it was in 2002 to 2005 would be progress for us.

Senator BURR. Does that mean you negotiated a bad deal for the last 4 years?

Mr. WHITAKER. I don't think so. It means FDA needs to do a better job, and we're committed to helping them get there.

Senator BURR. You can't answer the question that they got almost 100 percent, and you're getting back to historic norms with what you're negotiating in the next agreement, unless you negotiated a bad agreement before, or they would have been at historical norms then.

Mr. WHITAKER. The early part of MDUFA III, they were not doing as well as they are now. Over the course of the last 3 years, we've seen significant trends downward in every major category, which, to us, is progress.

Senator BURR. In fact, were they following the statute in 1997, they would have probably made improvements on historical norms.

Mr. WHITAKER. That's probably correct.

Senator BURR. Mr. Gaugh, you said that this was carefully negotiated for all companies. Correct?

Mr. GAUGH. Yes.

Senator BURR. The last agreement that has almost a year left on it—the FDA processed no backlog applications.

Mr. GAUGH. They have processed some backlog applications.

Senator BURR. The total number has not been reduced significantly. Correct?

Mr. GAUGH. That is correct. There's about——

Senator BURR. Did you negotiate a bad deal last time that didn't include all companies? If a company has got an unusually large number in backlogs, have you now covered them in the next negotiation where you didn't in the last one?

Mr. GAUGH. I think we have. We think we have, yes, because we learned a lot from our first agreement, which was GDUFA I, and a lot that we didn't know then. We've learned over the course of action negotiating GDUFA II for the past 3½ years, and from those learnings have determined that we are not leaving any ANDA applications behind. All are being pulled forward into GDUFA II, and all will have a goal date, and that goal date will be either 10 months or 8 months, depending on the priority or the standard review.

Senator BURR. Let me ask all three of you—last question. Would you be supportive if the committee designed some type of claw-back mechanism if, in fact, FDA does not meet their negotiated deliverables to the industry?

Ms. Holcombe.

Ms. HOLCOMBE. I don't think we would be supportive of that, Senator, because most—the vast majority of the funds that are paid in user fees in PDUFA pay for staff at FDA, and a claw-back could potentially have an impact that was adverse——

Senator BURR. I didn't say I was going to claw back your money. I'm going to claw back our money.

Ms. HOLCOMBE. Oh, appropriated money.

Senator BURR. We don't have to make as bad a deal as you guys have made.

Mr. Gaugh.

Mr. GAUGH. Yes, holding any industry accountable would make sense.

Senator BURR. Mr. Whitaker.

Mr. WHITAKER. I agree. Holding industry accountable would make sense. We like the agreement as it is.

Senator BURR. Well, let me say for the record that all the center heads sat at that table not long ago and said they wouldn't be opposed to us clawing back, either.

I thank the chair.

The CHAIRMAN. Thank you, Senator Burr.

Senator Franken and then Senator Hatch.

Senator Franken.

## STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman.

I'm going to echo Senator Murray a bit here. I've been doing roundtables around my State on the cost of pharmaceuticals, and there's been no question that this is really affecting people, the spike that we've seen in the last few years. These are high launch prices. There are price increases on older drugs.

Ms. Holcombe, you said this is complicated. Can you give me an explanation why this has happened in the last 3 years?

Ms. HOLCOMBE. Senator, I think what you're saying is what has happened in the last 3 years is that drug prices have increased at a rate or to an extent that is larger than increases in the total healthcare system, which is——

Senator FRANKEN. Well, yes, and also in the historic rate of pharmaceuticals. In other words, they were proceeding at a certain pace, and then there was a—I do sound effects with my questions—they went up. They spiked. What has caused that?

Ms. HOLCOMBE. We looked recently at the CMS data which just came out about 3 weeks ago. Those data do not indicate that drug prices have spiked. In fact, they indicate that there was a small spike in drug prices when the cure for hepatitis was launched and went into the marketplace and was very quickly adopted. Many more people than had been using drugs before were using that particular drug. Since that time, the increase in the cost of drugs parallels the increase in the cost of other services in the healthcare system.

I think you're asking a bigger question, which is just the general question of why do drugs cost so much, and it's not a question that I can answer for a whole variety of reasons, including that I'm not at a drug company, so I'm not sure of how this is calculated.

Senator FRANKEN. I understand. It's just—we need the answers. I mean, you're not an average American walking around, and you should probably have a better perspective on this than most people. That's why we need more transparency. We need more transparency in the drug supply chain.

You mentioned pharmacy benefit managers. They're a part of this. We have to look at deductibles and co-insurance, maybe looking at the value of a drug, the way that drug manufacturers offer discounts to customers, consumers, which encourages product loyalty, and then they—because they get these coupons—it costs the whole healthcare system more. Your organization will be part of this dialog, right, as we go forward?

Ms. HOLCOMBE. Yes, we are happy to be part of that dialog.

Senator FRANKEN. Can you commit that your organization and the companies that you represent will commit to doing everything they can to have transparency, to create transparency, so we can do whatever is possible to lower the cost to patients, out-of-pocket cost, and make these great drugs more affordable to patients?

Ms. HOLCOMBE. We will definitely commit to being part of the discussion about what can be done to make the system more transparent and to make the system work better for everyone.

Senator FRANKEN. When I say transparent—like on the research for—I hear industry say that the estimates of the cost of developing a drug may be as high as—they estimate like the average drug is $2.6 billion, and I'd like to see more transparency in that, because very often, we don't see what the NIH research did in creating the scientific knowledge that led up to some of the development of these drugs. We need to really look at this.

Mr. Chairman, I would suggest—I know that this is on the user fee agreements today, and I'm sorry to get off on this. This is something that when I go around Minnesota, it is on the minds—and I'm sure it's in your State. I'm sure it's all over the States. You go around—this is freaking people out. It really is. I would hope that

we could do a hearing on pharmaceuticals—on the cost of pharmaceuticals at some point.

Thank you. Thank you for allowing me to go over my time.

Thank you all.

The CHAIRMAN. Thank you, Senator Franken.

We'll go to Senator Hatch and then Senator Warren.

STATEMENT OF SENATOR HATCH

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

I appreciate the testimony of all of you here today, and, Ms. Holcombe, I appreciate the opportunity to discuss the user fees and the potential for a change within the FDA. After reviewing the user fees, I was particularly pleased by the thoughtful additions to the breakthrough therapies and rare disease programs in PDUFA.

Ms. Holcombe, could you please expand on the ways in which this agreement integrates rare disease experts into the review teams and what skill sets they can bring to the discussion that will promote a more complete perspective of rare drug approvals?

Ms. HOLCOMBE. Thank you, Senator. One of the key things that FDA will be doing under the PDUFA VI agreement will be integrating the rare disease program staff into the review of every application for a rare disease therapy. These rare disease program staff are people who work at FDA full-time on the topic of developing drugs and developing medical devices that are used for people with rare diseases. They do a lot of outreach into the rare disease community. They understand the patient needs.

They understand the diseases, and because these diseases are quite small, often it is the case that the medical review staff in a review division may not have encountered this disease before and may not have a lot of knowledge. Bringing these knowledgeable people into that review so that everyone can understand how this disease is affecting patients is going to be a crucial advantage for patients.

Senator HATCH. Well, thank you.

Mr. Whitaker, in this era of digital healthcare and the proliferation of the Internet of Things, more and more of the medical devices approved by the FDA are networked and, therefore, at risk to being compromised by bad actors. The Nation's hospitals have been warned that our enemies abroad seek to exploit them because of their cybersecurity infrastructure. The security of medical devices is starting to make headlines for the potential of jeopardized patient safety and privacy, and these devices could serve as an entry point to cause greater harm to the hospital network.

Mr. Whitaker, can you explain what the FDA is currently doing as they review pre-market applications to ensure that medical devices are secured in the best possible way? Do you believe or feel that the MDUFA IV agreement will better position the FDA and, in turn, the Nation's healthcare providers to have a greater understanding of the cybersecurity risk associated with any given network in medical devices?

Mr. WHITAKER. You raise a really important point. We work very closely as an industry with the FDA on broad policy parameters for cybersecurity. We recently unveiled our own AdvaMed medical technology group cybersecurity principles for our companies to fol-

low in developing those. We work with the FDA both on the policy side and on the approval and product development side.

Individual companies work directly with the FDA on each of those products to make sure that they're enhanced, secure as much as possible, and it's a very extensive process. This MDUFA agreement supports increased funding for cybersecurity activities and increased FTEs to make sure they're doing it in the right way.

Senator HATCH. Well, thank you.

Let me just ask this of all of you. Effective communication is essential to efforts to expedite drug development. We know that more productive communication leads to more efficient review and faster approval in the system. In the past, levels of communication with the applicants were different across centers and within different review divisions at the FDA.

How do these user fee agreements buildupon previous attempts to enhance communications, and how do they equalize treatment across centers for those industries whose business decisions are impacted by inconsistent communication? If you could just go across the table, I'd appreciate it.

Ms. HOLCOMBE. Senator, one of the things that is in the goals of PDUFA VI is an evaluation by an outside third party of the communication practices across all of the centers in CDER and CBER, and the idea there is to have that outside third party determine what are the best practices, who's doing the best job and how are they doing it, and can you and how do you translate those practices across to be sure that we are minimizing inconsistencies across centers. It is, as you point out, crucially important for the development of new products to have this ongoing productive communication with FDA.

Senator HATCH. Well, thank you.

Mr. Gaugh.

Mr. GAUGH. As I mentioned in my testimony, we learned a lot from GDUFA I that we didn't have, and communications was a big part of that. We built into GDUFA II information requests from the FDA to industry, division review letters from the industry. We also built in the complex products where we have pre-development meetings, pre-filing meetings, and then mid-cycle meetings. All those communications are enhancements in GDUFA II.

Mr. WHITAKER. Similar to the others, there are two independent assessments in the MDUFA agreement that go both at the operations and the goals of the letter, but also to ensure that there's better communications between the centers hitting the outcomes that we've set forth.

Ms. BENS. I would just add from the patient perspective that we don't need the independent assessment to show us that the different divisions at FDA really are being responsive to patient needs, and that's really a product of the fact that there was so much attention placed in PDUFA V on patient-focused drug development. All the centers are incredibly responsive to organizations like ours, and we engage with them.

Senator HATCH. Well, thanks to all of you. I really appreciate your testimony.

Sorry I went over, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Hatch.

Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman and Ranking Member Murray.

The FDA makes sure that devices we use and the drugs we take are safe and effective. The FDA makes sure that our blood supply is secure. The FDA makes sure that our food is safe to eat. The FDA makes sure that nutrition labels are accurate. In these and many, many other areas, the FDA is the cop on the beat, getting innovative and important products to market and at the same time trying to keep Americans safe.

I don't understand why one of the first things that President Trump did when he took office was to start cutting the number of people at the FDA. A few weeks ago, I asked FDA officials about the Federal hiring freeze that the President has imposed on the agency. Those witnesses indicated that while some FDA positions had been granted exemptions, others had not.

Ms. Holcombe, am I correct that the proposed prescription drug user fee arrangement funds about 230 new positions at FDA?

Ms. HOLCOMBE. Yes, Senator, 230 new positions over the course of the 5 years of PDUFA VI.

Senator WARREN. Right. Why does the FDA need those new positions?

Ms. HOLCOMBE. To carry out the goals of PDUFA VI and to continue to meet all of these goals that have been in place for almost 25 years to enhance drug development and to be sure that the review is efficient and——

Senator WARREN. So this is about expediting the review of drugs, basically.

Ms. HOLCOMBE. Yes.

Senator WARREN. Does it worry you that at the same time that we're trying to boost the number of staff implementing the FDA's mission that the President is trying to cut the number of FDA staff by preventing the agency from filling vacant positions and by enacting mid-year cuts?

Ms. HOLCOMBE. It worries me that a hiring freeze would prevent FDA from filling vacancies and hiring new positions that we believe, through our negotiations and our understanding of how many people it takes to change a light bulb, are needed to achieve the goals of PDUFA VI. It may be not 100 percent recognized that PDUFA fees pay for the staff who work on PDUFA activities.

Senator WARREN. Right.

Ms. HOLCOMBE. This is money that fee payers are paying into the agency. That money is paid in those fees by statute, so it's not like, well, we're not going to collect them anymore. We have to pay the fees. The fees are for hiring people. If people can't be hired, the fees can't be spent. That's not a good thing for anyone.

Senator WARREN. All right. But for very specific purposes, and that's why it is that I'm concerned about this. In addition to the hiring freeze, President Trump's budget blueprint calls for cutting congressional support by as much as a billion dollars for the FDA next year, and now President Trump says he wants to cut $40 mil-

lion from the FDA's budget in the current year, which has only 5 months left in it.

Ms. Bens, when drug and device companies negotiate user fee agreements with the FDA, they get to pick and choose what gets funded. Is that right?

Ms. BENS. That's correct.

Senator WARREN. For instance, if they don't want to fund post-market surveillance programs to track how devices are performing once they've been implanted in patients, they can just refuse to let their fees go toward those activities. Is that right?

Ms. BENS. For the purposes of the establishment of the NEST for post-market activities, that would be funded out of appropriations.

Senator WARREN. If appropriations is cut, then there's less money for that.

Ms. BENS. Correct.

Senator WARREN. What about the FDA's public health work on issues like tobacco use or food safety or keeping the blood supply safe? Do the medical product user fee agreements fund that?

Ms. BENS. Largely, they don't. Actually, budget authority appropriations still fund about 30 percent of the medical device review activities at the FDA and almost 50 percent of what's done for devices. A lot of activities that fall outside of the agreements would have to be sacrificed.

Senator WARREN. OK. President Trump seems to think that user fees are a substitute for Congress doing its job. He's wrong on this. They are a supplement, not a replacement, and if we take away FDA funding, the result will be a crippled agency, a cop that is severely underfunded and whose ability to enforce the law will be at the mercy of whatever the regulated companies do or don't want to see enforced. That's a recipe for disaster.

The FDA needs the employees, and it needs the resources to be able to do its job.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Warren.

Senator Young.

## STATEMENT OF SENATOR YOUNG

Senator YOUNG. Thank you, Mr. Chairman.

The FDA's Sentinel initiative was expected to transform patient safety by using claims data and other real-world health information to find drug safety issues. However, as the *Journal of the American Medical Association* points out, only a handful of FDA safety actions have resulted from Sentinel, and use and awareness of the system within the FDA is generally low. Despite years of investment, Sentinel has not yet become the active drug safety surveillance system that we envisioned.

Ms. Holcombe, how can PDUFA VI, that agreement, improve upon Sentinel, given the issues raised?

Ms. HOLCOMBE. Thank you, Senator. Under PDUFA VI, Sentinel will be expanded, and it will be integrated with the entire set of drug safety system initiatives at FDA. There will be additional training; there will be additional staff brought on board at FDA; and FDA will be interacting more proactively with the outside com-

munity, including drug developers, patient groups, and others, about its use of Sentinel and how it's using it.

In the beginning, Sentinel was a pilot program. It has now expanded to its full capacity and will continue to expand during PDUFA VI. Under PDUFA VI, additional user fees are being paid by our industry to the tune of $50 million for this expansion of Sentinel, because, as you suggest, it is a significant, huge source of drug safety information and needs to be expanded and used effectively.

Senator YOUNG. Thank you.

Mr. Whitaker, Ms. Bens, Indiana is not only a major pharmaceutical producer, but also a major producer of medical devices. Building on that last question, did you insist that the FDA use lessons learned from Sentinel before funding the NEST program?

Mr. WHITAKER. It was part of our conversations as well, connecting those. We feel like—we support the NEST program and the activities around real-world evidence, particularly to help in the pre-market activities, but, eventually, more information. We believe there are lessons from Sentinel that can be carried over, and we did encourage them to reflect back on that.

Senator YOUNG. Any particular lessons you want to hit on?

Ms. BENS. I'd say one of the most important things—in the early days of the Sentinel initiative, you had to send queries into the system to get information back about different safety signals, so you had to know what question you wanted an answer to. With NEST, because it's going to be incorporated into the whole healthcare delivery system, it's going to provide in the end more real-time information. It's a more active system, and I think that that's one of the major benefits of moving in that direction.

Senator YOUNG. Thank you.

Ms. Holcombe, Ms. Bens, Mr. Whitaker, are there particular metrics that should be put in place that perhaps you already have in mind to implement so that we will know whether or not the resources dedicated are actually successful in improving NEST and improving the Sentinel initiative and so forth? How do we measure success moving forward?

Mr. WHITAKER. Broadly, in the entire agreement, there are a whole series of reporting requirements from the FDA to Congress and to us as well that go to whether or not they're meeting the intended purpose of each of the provisions that are included, and I assume that applies to NEST as well. Whether it's time for decision or approval times or process improvements, all that should be reported back, I believe, on a quarterly basis to Congress and the industry so we can assess whether or not it's effective and working.

Ms. HOLCOMBE. One of the key things about Sentinel is that because of the size of the database, it is, as Ms. Bens suggested, extremely difficult to use. It's complicated. You have to develop a question. You have to know how to ask the question. It was always envisioned—from the very beginning of Sentinel, Congress envisioned that this would be a national resource.

One of the important components of PDUFA VI is for FDA to encourage the data partners of Sentinel to work with outside people so that other people can query this massive database. Those processes to allow other people to query this database are being devel-

oped now, and FDA is very supportive of them. At the end of this 5 years, it will be really great to look back and see how that has progressed.

Senator YOUNG. Very good. One final question, Ms. Holcombe. In a previous user fee hearing, we heard from FDA about its plans to incorporate more real-world evidence in regulatory decisionmaking related to safety and efficacy. What additional clarity needs to be provided to sponsors or challenges need to be addressed in order for real-world evidence to be effectively incorporated into the regulatory decisionmaking process?

Ms. HOLCOMBE. Sponsors need to understand the extent to which this real-world evidence can be converted into the kind of substantial evidence of safety and effectiveness that FDA requires. For example, we do know that real-world evidence often is the source of safety information. We need to do it the right way and so forth. The question is can we use—can we tap these massive data resources? Can we tap people's Apple watch? There's a lot of information out there. Can we tap that to learn about how drugs are working, in other words, about their effectiveness, so that those data could add to clinical evidence for, say, a new indication for a drug?

One of the things that is going to happen under PDUFA VI is there is going to be a workshop, a series of public meetings, and then a pilot program at FDA where outside experts are going to help see whether we can use these data in these different ways.

Senator YOUNG. Fascinating times. Population health data to inform some of the work you do. Thank you.

The CHAIRMAN. Thank you, Senator Young.

Senator Hassan.

## STATEMENT OF SENATOR HASSAN

Senator HASSAN. Thank you, Mr. Chair and Ranking Member Murray.

Good morning to the panel. Thank you all very much for being here.

Because there's been some discussion of it already, I don't want to belabor the issue of drug pricing transparency, but I will add my voice here. I just got back from my home State, where I heard from a constituent whose cancer treatment, if he chose the most up-to-date treatment recommended by his doctor, would cost him $34,000 out-of-pocket after his Medicare cost for the year. It's just something he can't afford.

As a former Governor, I can tell you what pharmaceutical prices did to my State budget. To the people I hear from, whose young children are having sudden new allergic reactions and have to pay $600 for an Epipen, the average cost increase doesn't matter to them when you're not part of the average, right?

I am concerned that—Ms. Holcombe, in your testimony, you talk about the importance of transparency in the FDA expenditures with the user fees. I agree that that's very important. I also think Americans need to understand, and the industry needs to disclose, research and development cost, marketing cost, manufacturing cost so that we can have a common understanding of what really is driving the pharmaceuticals and address it.

I know you all want to work on that, but I just wanted to let you know that I'm with a lot of these folks. I'm hearing about this every day from constituents, and it really is impacting their livelihoods, their lives, their futures in really impactful ways.

Having said that, I want to move on to a question for Mr. Gaugh about something else I hear a great deal about. In New Hampshire, the opioid epidemic continues to devastate our State. One of the important tools used to help address the epidemic is the risk evaluation mitigation strategy, or REMS, for opioids. REMS helps to try to minimize the risk associated with these medications. I would argue that we need stronger REMS for opioids, and I'm hopeful that the FDA will strengthen the REMS for extended release and long-acting opioids when they update it.

Currently, for extended release and long-acting opioids, the REMS requires opioid manufacturers to make training on proper prescribing practices available to healthcare providers who prescribe these products. The FDA reports that around 66,880 providers had completed the training as of February 2016. The goal for 2017 is to have 192,000 providers trained. It looks like the FDA is on track to fall well short of that target.

There are about 320,000 active prescribers of extended release and long-acting opioids. That means only about 21 percent of active prescribers have gotten training. We have, clearly, a long way to go.

Dr. Gaugh, drug makers in your industry who manufacture extended release and long-acting opioids are required to make this training available to prescribers. Aside from meeting the minimum in actually making it available, I'd like to understand if your industry is taking proactive steps to increase the number of providers who are trained on proper prescribing of these products.

Mr. GAUGH. Thank you, Senator. Yes, besides the companies themselves doing this, we have just recently at AAM launched a program that will reach out to all schools, so 0 to 12, and then universities as well, to educate the American public and the patients who are also using these medications, but, in addition to that, to educate the prescribers as well. We've just launched that about 3 months ago.

Senator HASSAN. Thank you. In addition to wanting to make sure that we are addressing the high price of pharmaceuticals and devices as well, I also understand how important the products are to people's health. My son has about 10 medications and a medical device, and they have increased his quality of life enormously. So I am very grateful.

Because I know what a difference your products make, I recognize that a sustained, robust investment in biomedical research at the NIH is critical to developing new treatments and improving the lives of patients. Research funded by the NIH saves lives. It also generates economic activity. For example, last fiscal year, projects in my State of New Hampshire received $99 million in awards from the NIH, generating close to $239 million in new economic activity.

Ms. Holcombe, perhaps you could start by just commenting a little bit, because I know BIO represents biotech companies, academic institutions, and State biotech centers, and Federal investments in research at NIH are important to your industry and help drive in-

novation. The President's budget has proposed a 20 percent cut to the NIH budget. How would a 20 percent cut to NIH impact the patients served by your members?

Ms. HOLCOMBE. The impact would be disastrous. We agree with you completely about the importance of NIH research. It forms the basic building block on which we do our work. We develop the products, but we have to have this basic understanding of the disease first. NIH is the flagship of American science, and we think cutting its budget by that significant amount is not a good idea.

Senator HASSAN. Thank you very much.

Thank you, Mr. Chair, for letting me go over.

The CHAIRMAN. Thank you, Senator Hassan.

I'm going to go ahead with my questions. On a more hopeful note, the Appropriations Committee, thanks to the work of Senator Murray and Senator Blunt last year, recommended a $2 billion increase in National Institutes of Health funding, which was approved. They've recommended a second one, which, if we do our jobs properly, we might be able to approve by the end of this month, April. The 21st Century Cures legislation added another $5 billion. That's the path that many of us hope that we will be able to follow for the National Institutes of Health.

Let me get down to some brass tacks here. Senator Murray and I observed and you've observed that, typically, this is a bipartisan proceeding. There's been an enormous amount of work gone into this, many briefings, going back to 2015, a lot of good faith negotiation and discussion. You've done your job on time. Now it's up to us to do our job on time.

On time means, for example—and this isn't set yet—but if we were to finish our work in committee in April, which is this month, and take it to the floor of the Senate next month, which is May, that would leave time for the House to act and for there to be a conference, if necessary, by the end of July. We have to finish by the end of July in order to avoid expiration of the agreements on October 1. In other words, we have to finish before our home work period begins in August.

What would be the consequences, from your point of view—we heard last week from FDA, but what would be the consequences from your point of view if Congress fails to act by the end of July to reauthorize these agreements?

Let's start with you, Ms. Holcombe.

Ms. HOLCOMBE. It would be awful, and the reason——

The CHAIRMAN. In what way?

Ms. HOLCOMBE [continuing]. The reason is that there is a kind of moment in time, according to government personnel rules, where if FDA does not see that this reauthorization is moving forward and predictably will be achieved by the end of September, they will have to notify their staff that their jobs may be in jeopardy.

The CHAIRMAN. Would you assume that moment would be reached if Congress hasn't acted by August the 1st?

Ms. HOLCOMBE. Yes. I am assuming that it is sometime in that timeframe, yes.

The CHAIRMAN. Mr. Gaugh.

Mr. GAUGH. It would be devastating to the generic industry if this was not to pass.

The CHAIRMAN. In what way?

Mr. GAUGH. If you go back to appropriations—and Senator Warren made that comment—in the generic industry, appropriations pay for about 320 FTEs at the agency to work on generic drugs. The user fees that we put in place will increase that by about 1,500 FTEs, taking the total up to about 1,830 FTEs. That's what we believe is needed to get the approvals at the level that we need them and to get the backlog reduced, No. 1, and to start hitting that 10- and 8-month metric.

The CHAIRMAN. Would you agree the end of July sounds like the point before which we have to finish our work?

Mr. GAUGH. Yes. Dr. Woodcock has already stated that at the end of July, first of August, if it's not passed, she'll have to start working on that furloughing process, whatever that might be.

The CHAIRMAN. Mr. Whitaker.

Mr. WHITAKER. We have the same concerns, and I think the timeline you outlined is right. I would associate myself with the remarks of Dr. Shuren. If he suggests that a third of the workforce would be lost, that's a huge hit to our industry. Broadly, it creates tremendous uncertainty for our industry, and, in many ways, uncertainty is really the enemy of innovation. When you get hit with that uncertainty, it freezes companies. We would want to move this as quickly as we can. I think the timeline you've outlined is right.

The CHAIRMAN. Ms. Bens, from a patient's point of view?

Ms. BENS. I would say that the impact is probably going to happen sooner than the summer, because we tend to focus on the morale of employees at the agency, which is something that is not always talked about. These are really dedicated Federal employees, and when we interact with them, they just want to do their job to keep people safe and to get drugs to market that are going to benefit them. When they hear that their jobs are in jeopardy and potentially at risk, it makes anyone's position feel almost inadequate. I would just continue the momentum as quickly as you can, because it's going to be beneficial to not just the direct impact that user fees are going to have, but also to keep morale high.

The CHAIRMAN. Thank you, Ms. Bens.

Senator Kaine.

## STATEMENT OF SENATOR KAINE

Senator KAINE. Thank you, Mr. Chair.

I want to echo—first, thanks for being here today—the comments of my colleagues on both pricing issues and Senator Warren's comments on the possible consequences of a hiring freeze, and I want to return to Senator Hassan's questions about the budget.

I appreciate the chair's comments about what the appropriators are likely to do or hope to do, and I hope that that's the case. I would like to ask the other witnesses—Ms. Haycombe was asked about the potential effects of a $6 billion cut in NIH to medical innovation. Many of the products that the FDA approves begin with or are connected to some NIH funding. Do you share her view that a budget cut of that magnitude to the NIH would be devastating to medical innovation?

Mr. WHITAKER. Yes, I share that view. It's a really hard hit to us. It would be a negative impact across the board on the entire

industry, and at the end of the day, patients will be hit by that, and that's the concerning part. I will go back to what the Chairman said. It's encouraging, however, that the direction the Chairman is taking, that Congress is taking not to support that level of cuts makes us feel much better about the prospects of the next year or two.

Senator KAINE. I'm sorry, Ms. Holcombe. I said Ms. Haycombe. It's Ms. Holcombe. Excuse me.

Mr. Gaugh or Ms. Bens.

Mr. GAUGH. Very important, because the innovative drugs of today are the generic drugs of tomorrow. If those are devastated in any way, that would also devastate the generic side of the business as well.

Senator KAINE. Ms. Bens.

Ms. BENS. I'll just highlight an example. One of the areas that we work with the FDA on is trying to accelerate the clinical trial process for Alzheimer's disease. About 2 years ago, FDA released a report talking specifically about challenges with Alzheimer's disease development, and all of the areas that they identified were related to a lack of understanding about the disease process and other areas where basic science and NIH research can really help fill the gap. This is now the time that we really should be investing and filling those research gaps to get at better treatments.

Senator KAINE. Ms. Bens, let me stay with you. You discussed the importance of patient interaction with the agency. How do the user fees that have been negotiated in the agreements that are on the table now—how do they improve the process of patient interaction with the agency?

Ms. BENS. Absolutely. One of the major things that came out of the last user fee reauthorization was a series of meetings where you could incorporate patient perspectives into the drug development process to get FDA to really understand about a disease. What the next user fee agreement is going to do is allow groups like ours to really learn how you can take that information about what patients are experiencing and develop endpoints for clinical trials.

This is something that's new for organizations, but we're actually working in this area for one particular disease. We're working directly with the FDA to take patient information to develop an endpoint that can be used by companies or anyone looking to develop a drug for a specific treatment. We're really excited about it, and PDUFA VI will help with that.

Senator KAINE. That's great. I was on the Aging Committee in the last Congress and was lucky to get drafted to be on HELP in this Congress. In the Aging Committee, we spent a lot of time shining a spotlight on the particular problem of spiked pharmaceutical prices in rare diseases—orphaned diseases and orphaned drugs—and there was sort of a business model that was not reflective of the industry, generally, but a business model of kind of patients as hostages.

If there's a disease that's relatively rare, and there may only be one drug that could treat the disease, companies that weren't really health companies at all—they tend to be more hedge funds—would buy this particular drug and then dramatically jack the prices up.

It just points out the challenge of rare diseases, diseases where the number of people who have the condition are so small that they can be an obstacle to the development of multiple treatments and development of competition.

Could you elaborate on the provisions of PDUFA VI and how they might impact the rare disease community and the development of orphan and breakthrough drugs? Because that is of significance, even if a particular rare disease may only affect tens of thousands. I think 25 million to 30 million Americans, in total, are affected by rare diseases. Talk about PDUFA VI and how it would help us deal with this problem.

Ms. HOLCOMBE. One of the things that will be done under PDUFA VI, Senator, is that experts at the FDA who are currently in the rare disease program—and these are people who are medical professionals as well as other kinds of staff at FDA who understand rare diseases—interact frequently with the community and are up to speed on the nature of the disease. Those people will be integrated into the review of every rare disease product application.

That will help enormously, because, quite often, what slows down this review is a lack of understanding of what this disease is, because if it only affects a few—tens of thousands of people—the chances are that the vast majority of doctors have never seen a person with this disease. They don't have this deep understanding of what the needs are. How does this disease affect the patient, and what kind of product attributes are going to serve best that population of patients?

The CHAIRMAN. Thank you, Senator Kaine.

Senator Cassidy.

Senator CASSIDY. Do we have another Democrat to go and I can collect myself?

The CHAIRMAN. Senator Casey.

## STATEMENT OF SENATOR CASEY

Senator CASEY. Thank you, Mr. Chairman.

I want to incorporate by reference much of what's been said already with regard to the hiring freeze and NIH investment. I couldn't agree more with the sentiments that I think are bipartisan. I won't ask a hiring freeze question because that's been covered. I may ask one for the record to amplify some of these concerns we have.

I wanted to focus on biosecurity. We've seen just in the last couple of years, whether it's Ebola or Zika or any other threat, how important this area of the law is. We know that the Pandemic and All Hazards Preparedness Reauthorization Act of a couple of years ago, 2013, contains important provisions to both modernize diagnostic and treatment capabilities. And just for the purposes of this question, putting aside the FDA's emergency use authorization, I want to explore how the proposed user fee agreements will accelerate innovations in drugs and devices that can be used to address these public health emergencies.

Mr. Whitaker, I'll start with you. Can you comment on how these user fee agreements, the proposals, advance the development and approval of diagnostic devices and novel treatments?

Mr. WHITAKER. I mentioned this earlier, and let me just step back and say from our perspective, a user fee agreement and a well functioning FDA hits right at that point. If you have a clear, a transparent, and a predictable process to get—whether it's medical devices or diagnostics—to the market, it makes the whole system function better. The premise of this entire agreement is around making it more clear and more transparent.

Part of what we focused on was driving down the time to decision goal so that those products would get to patients sooner, and our focus will continue to be on that with the FDA, and also helping small companies who have new and emerging technologies, many of which may be in this space, get through the process sooner as well at a lower cost. Much of that is captured in this agreement, and it hits directly and somewhat indirectly at your question.

Senator CASEY. Thank you.

Ms. Holcombe, the same question.

Ms. HOLCOMBE. There are some key initiatives under PDUFA VI that will have a direct impact on those kinds of products, Senator. One of them is the increase in the number of staff that will be devoted to the review of what are called breakthrough therapies, and breakthrough therapies are defined as drugs that have a high unmet medical need or, in this case, a high unmet public health need, and the breakthrough therapy program will definitely benefit these kinds of products.

In addition, FDA is maintaining its goals of a 6-month review after an application is accepted for a priority drug. This is separate and apart from the emergency procedures, but this is in sort of the normal course of events, that FDA identifies a drug as being a high-priority to get this drug out onto the market as quickly as possible, and these drugs will fall into that category as well.

Senator CASEY. Thank you.

Mr. Gaugh or Ms. Bens, anything on this you want to add?

[No verbal response.]

Senator CASEY. I wanted to move as well—I know I have a little more than a minute, and I might defer most of this for a written question. With regard to medical device safety, the National Cardiovascular Data Registry detected a potential safety problem that was highlighted in a *New England Journal of Medicine* report. They highlighted a safety problem in the device used in cardiac procedures. The registry was able to identify the safety alerts within 12 months, yet some healthcare sectors are less accustomed to using data systems to monitor device safety after approval.

Mr. Whitaker, I'll start with you again. How does the medical device industry plan to support efforts to collect meaningful data from patients to inform the safety profile of medical devices?

Mr. WHITAKER. This agreement—we fund two specific things. One is the patient engagement component of that, which is a direct component of our user fees to support patient engagement, and second is the NEST program, where you'll get that evaluation system set up. This agreement has $30 million dedicated specifically for that, which includes funding for the coordinating center and also additional FTEs at FDA to help support those efforts.

Senator CASEY. Thanks very much, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Casey.

Senator Cassidy.

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. Mr. Whitaker—I feel like Saint Paul seeing through a glass darkly, so what I'm about to speak of, I'm not sure I entirely understand, but I'm kind of groping toward my understanding. I get a sense that in these complex drugs in which a device is needed to deliver a drug that sometimes even after the drug is off patent—think Epipen—that minor modifications of the delivery device serve to evergreen the product, that the minor modification of the device then becomes a reference at which point the generic has to catch up with the delivery device. Even though epinephrine has been around for decades, nonetheless, there's an evergreening of the product. Are we in agreement so far?

Mr. WHITAKER. I think so.

Senator CASSIDY. I guess my question is—that seems inherently biased against the consumer. If you were corrected by your assistant, I'll accept the correction.

Mr. WHITAKER. No, I was asking—this is, in many ways, not necessarily a medical device issue, but more of a drug product issue.

Senator CASSIDY. If we're speaking of epinephrine, epinephrine is truly a—it's been around forever. I guess my question is how do we, as policymakers, encourage FDA through this process to not reward incumbent industry when, again, something which is not paradigm shifting but rather minor modifications serves to evergreen a product. That's a question.

Mr. WHITAKER. I don't know that I can answer that today.

Senator CASSIDY. That's a bad sign.

Mr. WHITAKER. In the case of Epipen, right, that's not a product that comes from one of the companies that we represent, and——

Senator CASSIDY. But speaking conceptually.

Mr. WHITAKER. Conceptually, I guess I would defer to the pharmaceutical or the biotech and the generics industry to talk about it more specifically as a combination product, which is essentially, I believe, what it is.

Senator CASSIDY. OK. Anybody have a comment?

Ms. HOLCOMBE. One of the things that is included in PDUFA VI, Senator, are some commitments by FDA to improve their processes for the review and approval of combination products, and if it is the case that the drug part of a combination product cannot be approved because it is being—the approval is being held up by the device part of the combination product, this is a process issue. It may be a design issue in the medical device as well, but I think one of the things that——

Senator CASSIDY. Can I ask you on that—because, again, my understanding is that if there's a modification of the device, the modified device now becomes a reference product, which means it becomes a moving target for the generic manufacturer to reproduce. Is that a fair statement?

Ms. HOLCOMBE. That definitely can be the case, yes.

Senator CASSIDY. In which case is it wise policy, then, for us to make the—not the new and improved, but rather the original device as the reference point, and that the new and improved has to work, but that the generic manufacturer could make the original—

if you will, whatever is the standard by which a generic is judged always lags by one, the new and improved. Do you follow that?

Ms. HOLCOMBE. I think I follow your question, and the answer is I don't exactly know the answer because we have to understand the reason for the change in the delivery device.

Senator CASSIDY. We know that there are devices which are paradigm shifting, and we know there's devices which are merely minor modifications. I'm not sure I'm going to accept what you just said, because sometimes we do know it's a minor modification and, demonstrably, it evergreens.

Ms. HOLCOMBE. It's possible that that could happen. I believe that is the case in this particular situation. I don't know the answer to the question of whether FDA should allow the generic to cite the original—quote, unquote, "original" reference, which is the drug in the original delivery device, whether that is even possible under the statute.

Senator CASSIDY. The question is we have to investigate that to see if that's possible.

Ms. HOLCOMBE. Yes. The second thing is if it is legally possible, then the process changes that are going to take place with looking at how combination products are evaluated across the board are going to be helpful, because this conversation is going to happen at FDA. Why don't we just let them put the epinephrine in this other pen? That conversation can happen, and there might be a completely 100 percent good reason that that can't happen.

Senator CASSIDY. We should force the conversation because we can imagine——

Ms. HOLCOMBE. Yes.

Senator CASSIDY [continuing]. Sometimes it would.

Ms. HOLCOMBE. Yes.

Senator CASSIDY. I am over. I yield back. Thank you.

The CHAIRMAN. Thank you, Senator Cassidy.

Senator Whitehouse.

## STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Thank you, Chairman.

One of the things about being the final Senator is that many of my questions have already been asked and answered. Let me just make clear to all of you that the value of U.S. taxpayer expenditures at the National Institutes of Health for medical research is very great and should not be cut. Is that a unanimous view?

[A chorus of yeses.]

Senator WHITEHOUSE. Yes, it is. OK. By the way, I appreciate very much the Chairman's comments in that regard. Particularly, with all the turbulence in Washington right now, for the Senate to act in a responsible way based on the appropriations that were passed last year and move through April without the drama of a government shutdown would be an important thing for us to achieve, and I think the people of the country would be grateful to not have that particular drama play itself out.

On a smaller scale, the witnesses have said that a failure to reauthorize would be awful and devastating.

Ms. Holcombe, the number that you gave of 230 FTEs lost—that's related to the President's proposed hiring freeze, correct?

Ms. HOLCOMBE. It would be.

Senator WHITEHOUSE. So there would be a different number related to a failure to reauthorize?

Ms. HOLCOMBE. No, that's—it would be the same number.

Senator WHITEHOUSE. It would be the same number.

Ms. HOLCOMBE. Right.

Senator WHITEHOUSE. Do you have an across-the-agency estimate for how many RIF notices would go out if we fail to reauthorize timely?

Ms. HOLCOMBE. A RIF notice or an announcement that there would be a RIF notice would go out to every employee who is funded by user fees.

Senator WHITEHOUSE. That is roughly how many?

Ms. HOLCOMBE. It's over 1,000 people in new drugs and more people in generic drugs and more people in devices.

Senator WHITEHOUSE. Do you know the number, Mr. Gaugh?

Mr. GAUGH. Over 1,500 in the generic space.

Senator WHITEHOUSE. We're up to 2,500.

Mr. Whitaker, roughly?

Mr. WHITAKER. Two hundred and seventy employees under MDUFA III, adding another 217 on top of that.

Senator WHITEHOUSE. So another 500, roughly?

Mr. WHITAKER. Yes, 500-plus.

Senator WHITEHOUSE. You get a pretty big number, a pretty big hit to the agency. I have two concerns about the degree to which this agency relies on funding by the industry that it regulates. One is fairly technical, and that is that the PDUFA fees support the prescription drug program, the medical device user fee agreements, MDUFA, support the medical devices, and we're seeing great growth in the combined drug device product area.

We've had trouble, although we've been told by both the drug and the medical device leads at FDA that there should be a third lane. We've had trouble getting anybody to try to design one that we could pass, and so the 21st Century Cures Act basically said to FDA, "Please try harder." It's not where we should best be, but it's where we are.

I worry that having the prescription drug industry fund through PDUFA and the medical device industry fund through MDUFA and nobody having a vested interest in the combined products could lead to a loss of interest in moving the combined product effort forward. What are your thoughts about that?

Ms. HOLCOMBE. I wanted to point out how generous the PDUFA agreement is to the medical device center for that very reason, because there are these difficulties in getting everything to happen at the same time, the device approved, the drug approved, and the product going out there for personalized medicine uses. Under PDUFA VI, there will be staff at the medical device center who are funded by prescription drug user fees so that the medical device center will have enough resources to be able to deal with these combination products.

Senator WHITEHOUSE. The other concern is that there are drugs—and opioids are an obvious example of this—where the issue of them being taken—safe when taken as directed doesn't really address the public health problem related to them because

of the danger of unauthorized use. We tried for a long time to try to put more pressure on the medical side to be more diligent about how opioids are prescribed. I can remember my daughter bringing home 40 Vicodin after her wisdom teeth were out. I think she got through three of them, and then that was it. We worked on that a lot in the CARA bill.

My concern is—and I guess this will be to the generic and pharmaceutical representatives here. Are you comfortable that FDA should look, where that is a concern, to those areas of unauthorized use, and do you see the PDUFA funding as a way to steer FDA away from considering those concerns?

Ms. HOLCOMBE. I'm not sure I understand your question completely. I don't think that the PDUFA funds would steer FDA away from those concerns, no. I think FDA, under PDUFA, is getting resources to allow them to review drugs and approve drugs that are safe and effective, and part of the safety of a drug is that, as you point out, it can be used safely so long as its used within its label. FDA also looks at whether it can be used safely if it's used outside the label. I don't think we're trying in any way, and I don't think we do with PDUFA funds, steer them away from that for opioids.

Senator WHITEHOUSE. Thank you.

Mr. GAUGH. I would echo the same thing for the GDUFA funds. They're not steered away. One more thing—and you might have stepped out of the room—AAM has launched a campaign for education of both the users and the prescribers about 2 to 3 months ago, and so that will go forward, and it's a multiyear campaign.

Senator WHITEHOUSE. I appreciate that. Thank you.

Thank you, Chairman.

The CHAIRMAN. Thank you, Senator Whitehouse.

Senator Murray, do you have additional comments?

Senator MURRAY. I do have one question. I've made it a priority to make sure women and minorities and older Americans are included in clinical trials so that we really understand how diseases impact those specific populations and make sure that any new treatments are actually working for them. I was very proud to work with a number of Senators here on provisions in the 21st Century Cures Act to require greater efforts by federally funded researchers to address the challenge.

Recently released data from FDA regarding industry trials shows that many drugs are still being tested predominantly in white men, even those intended to treat conditions that can have a disproportionate impact on women or minorities. In this era of precision medicine, it's really unacceptable not to know how these products actually work on the patients who need them.

Ms. Holcombe, I just wanted to ask you how are your member companies working to address those disparities, and how could using real-world evidence like that from registries and electronic health records help further that work?

Ms. HOLCOMBE. In addition to using real-world evidence and electronic health records, there's an important component of PDUFA VI that potentially will have a positive impact on this. It is extremely difficult to enroll clinical trials and we don't know all the reasons for that. Companies tend to enroll what they can and how they can.

One of the things that PDUFA VI is going to look at is innovative, new ways of designing clinical trials. One of the reasons that that could be helpful is that—for example, let's take the innovative design called the adaptive clinical trial.

This is a design where instead of just setting the endpoints at the very beginning and the people and who's going to be in what group and everything stays the same until the end, unveil the data, yes, it worked, no, it didn't—instead of doing it that way, what you do is you take a look part of the way through, and you can see, possibly, that there are some people who are responding to the drug and some people who are not responding to the drug, and then you can re-tailor the rest of the study according to those findings.

In the case of a drug that is working effectively in women, for example, but you have an insufficient number of women enrolled in a trial, if you design the trial so that you could find this out earlier on instead of going for 3 years until the end, then would that help you, and could you—and we have to use different kinds of statistics and all this, all of which you know—to analyze those data. That's something that seems to me might potentially be helpful.

I also agree with you that looking at real-world information, whether it's claims data or whether it's electronic health records, to determine how drugs are working in the real world setting, where doctors are giving care to real people, is a huge source of information that is largely untapped.

Senator MURRAY. Thank you very much, Mr. Chairman, for this hearing. We've heard a lot, but I think it's really important that we all remember in this process that we've got to put patients and families first, and the gold standard of FDA is a high standard, but it's one that we need to maintain.

I'm going to keep talking to you about post-market surveillance on medical devices—that's so critical to me—and, as you heard from my side, prescription drug prices. We understand FDA user fees is an issue, but that's one that our side continues to be extremely worried about.

The CHAIRMAN. Thank you, Senator Murray, and thank you for joining with me in calling the hearing and inviting the witnesses.

You did a terrific job today. It's very helpful to us. I thank you for the enormous amount of time you spent over the last several months getting the user fees ready for us. Now it's up to us to do our job and to do it in a timely way.

I'll make these observations. Tomorrow, we'll meet again, this committee, at 10 a.m. to hear from Dr. Scott Gottlieb, the nominee for the Commissioner of the Food and Drug Administration. It'll be an opportunity for me to ask him—I guess others may, too—about the hiring freeze at FDA.

I asked Dr. Califf what his top priority was from FDA's point of view for the 21st Century Cures Act. He said the ability to hire and pay personnel so that they could properly review the applications that come to the FDA, and we approved that by a wide margin.

Should Dr. Gottlieb be confirmed, which I hope he is, one of his first orders of business should be to review with the new administration the importance of allowing the FDA to take advantage of the new authority it has to hire the people it needs and pay them

what it needs so that we can get these lifesaving drugs and devices through the system and into medicine cabinets and into doctors' offices all over the country.

Second, as far as the President's National Institutes of Health number, it is reassuring to remember that Presidents' budgets don't normally end up being in law. I remember last year, President Obama recommended cutting the National Institutes of Health discretionary funding by $1.1 billion. Congress increased it by $2 billion and even added one-time funding in the Cures bill, which we hope we can approve this month.

Congress has a pretty firm attitude on the National Institutes of Health funding. It's a top priority for us this year, and I believe it will be next year, and Senator Murray working with Senator Blunt deserves much of the credit for what's happened in the last couple of years on that.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time if they would like.

Thank you for being here today. The committee will stand adjourned.

# ADDITIONAL MATERIAL

RESPONSE BY DAVID R. GAUGH, R.PH. TO QUESTIONS OF SENATOR CASSIDY

*Question 1a.* How many ANDAs filed prior to October 1, 2012 (GDUFA start date) for non-biologic complex generics are currently awaiting approval?

Answer 1a. It is unclear how many complex products are currently under review. That information is not shared with industry.

*Question 1b.* Is there a transparent way for generic manufacturers to identify where a lack of competition exists?

Answer 1b. Generic manufacturers have various methods and means of determining market opportunities. There are resources that are publicly available, such as the Orange Book, and other resources that are privately available to assess market share and market opportunities. There is no single method that can be used to make the determination of whether or not to invest in years of product development research. Such a decision is influenced by a range of factors, including the cost of marketing, uncertainty of a timely FDA approval, projected market share, and potential future mergers and acquisitions that may impact the overall company's portfolio—each of which play an intricate role in a company's decision to invest or not invest in a particular product.

*Question 1c.* How many of those applications would you anticipate receiving final approval in 2017?

Answer 1c. Because specific pending applications are only known to FDA, and the filing company, AAM is not privileged to these details. Therefore, we are not able to provide a response to this question. It is industry's hope that with GDUFA, FDA will be able to work toward an action that result in a final approval in a more consistent and timely manner to improve patient access to affordable medicines.

*Question 2.* Do you agree that lack of engagement and collaboration between the FDA and the applicant during the review phase for complex generic approvals contributes to lengthy and delayed reviews? If the FDA outlined how it will test these important products for bioequivalence, could we increase competition? Additionally, if the FDA was up front with generic manufacturers in this way, would we see more timely approval and availability of generics for complex products, and greater review efficiency at the FDA (products being approved in fewer than the current average of 4)?

Answer 2. Greater communication and cooperation between FDA and generic drug sponsors benefits both parties. Greater communication and transparency earlier on during the research and development process will increase the sponsors' understanding of FDA's expectations. For instance, having bioequivalence guidances for products shortly after an NDA is approved will provide clarity to the FDA expectations to ensure ANDA sponsors meet the quality standard requirements for approval. The increase in understanding will increase the quality of the submission. This, in turn, will only contribute to the improved timelines of the review and approval process for ANDAs. Industry's goal in GDUFA is not merely for faster FDA review timelines, but rather a more effective and consistent review process which will eliminate duplicative work and increase first-cycle approvals.

*Question 3.* In 2016 FDA issued a draft guidance to implement section 7002 of the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which provides that biologic products approved under section 505 of the Food, Drug, and Cosmetic Act ("FDCA") shall be deemed to be licensed under the Public Health Service Act *on March 23, 2020*. The draft guidance states that FDA will not approve an application submitted under section 505 for an impacted product, like insulin, which is pending *on March 23, 2020*; rather such applications will need to be withdrawn and resubmitted as a biologics application. Do you agree that the effective outcome of FDA's draft guidance will result in a dead zone during which development, review and approval activities will come to a standstill for potentially a period of several months to years for products like generic insulin? Do you agree, as is stated in the draft guidance, that the guidance will have a "significant impact" on product development, inhibit competition, delay product approvals and thereby increase healthcare costs?

Answer 3. AAM requested FDA[1] amend its proposed policy regarding pending applications because it erects unnecessary roadblocks to the development of transitional biologics, significantly delaying the approval and availability of lower cost, safe and effective biological products for patients in need. As FDA acknowledges, its proposal could have a "significant impact" on ongoing development programs for important transitional biologics, such as insulin and human growth hormone. FDA's proposed policy regarding pending applications will impede the timely approval of competing products in several ways. First, FDA's proposed policy will interrupt ongoing review activities for pending applications in a manner that will be highly disruptive and cause unnecessary delays. Second, FDA's proposed policy will force sponsors who are ready to submit applications for lower cost biologics prior to March 23, 2020 to delay their submissions until after March 23, 2020. This will significantly delay the review, approval and availability of more affordable biological products that compete with expensive brand name biologics.

The delays caused by this regulatory "dead zone" will not only have a significant impact on ongoing biosimilar development plans, but also will have a major negative impact on the U.S. healthcare system. For example, in the insulin market, FDA's proposed policy could result in $6.65 billion potential lost savings per year to the U.S. healthcare system.

Sanofi's Lantus and Lantus Solostar products are daily, chronic use medications widely prescribed to a growing population diagnosed with diabetes. In the year ending in October 2015, Sanofi Aventis realized almost $9 billion in sales—much of which was borne by State and Federal drug purchase and insurance programs—and the price is skyrocketing. According to a recent article in the *Philadelphia Inquirer*, the price of Lantus rose 22.7 percent in just 1 year, from 2014 to 2015. This increase was on top of two other significant price increases in 2013. A biosimilar or interchangeable insulin product approved to compete with the Lantus products alone could result in $18.3 million in daily savings to the U.S. healthcare system.

FDA's proposed policy thus has the potential to add billions of dollars of unnecessary costs to the U.S. healthcare system, with no countervailing public health benefit for patients. The only beneficiaries of FDA's proposal will be the sponsors of brand name transitional biologics, who will continue to reap monopoly profits during the unnecessary delays caused by FDA's proposed policy. This runs counter to one of the main objectives of the BPCIA, which is to increase patient access to safe, effective and affordable biosimilar and interchangeable biological products.

*Question 4.* Penetration of small molecule generics took decades—the Hatch Waxman Act was passed in 1984, but as recently as 2004, barely more than half of all prescriptions were filled as generics. While these products can drive patient outcomes, patients pay about 30 percent coinsurance and costs to Medicare are substantial—the 20 most expensive drugs accounted for 92 percent of Part B spending in 2013. We have a second shot at this transition.

Mr. Gaugh, as these innovative therapies lose patent protection, how can we expedite the shift toward lower cost biosimilars that could reduce patient cost sharing? Where are your education programs for patients and providers facing challenges?

Answer 4. Provider education is critical to allow for confidence in the safety and efficacy of biosimilar products. The issue was discussed at length during the BsUFA II negotiations, and the FDA agreed with AAM and the Biosimilars Council on the importance of continued outreach. The Agency's creation of the dedicated "Biosimilars Unit" will allow for increased education and outreach functions to patient and provider organizations. We look forward to continued efforts to amplify and assist the Agency in these efforts. In addition, Members of Congress, the agency, and industry must also address the continued concerns with biosimilar sponsors' ability or inability to obtain sufficient quantities of a biologic to perform the required tests and analysis to ensure the performance of the biosimilar product will meet the stringent FDA safety and efficacy requirements for biologics. There continues to be significant abuse of the REMS with ETASU and other, voluntary, restricted distribution programs. As such, biosimilar companies are often unable to acquire the samples they need to develop and test biosimilars.

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[1] GPhA & Biosimilars Council comments on Docket No. FDA-2015-D-4750; Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009. May 13, 2016.

## RESPONSE BY SCOTT WHITAKER TO QUESTIONS OF SENATOR CASSIDY AND SENATOR BENNET

### SENATOR CASSIDY

*Question 1.* The literature often speaks of the activated patient—one engaged in their own health care. Ideally, each patient would be engaged in their own health care decisions, and would choose the most efficient expenditure of their health care dollar. However, in health care, a given patient may have a plethora of options from which to choose—this can be very true in the device space.

Patients are seeing an increasingly crowded field of devices. However, it is very difficult for a typical patient to find the device that would produce the best value for somebody with similar health status. As a provider for 30 years, I can tell you that providers are in the same boat—data on outcomes for medical products and services certainly exist, but are not readily consumable.

For drugs, the FDA uses a rating system to differentiate between drugs that provide a substantial improvement over current standards of care—priority rated drugs—and those that bat par with existing options. While there is little reward for those more substantive improvements today, this priority rating system has been well developed between patient groups, clinical experts, industry, and the FDA—and serves as a clear signal to the market and to patients.

Mr. Whitaker, could a parallel effort by the FDA in the device space help us identify those devices which show big steps forward in patient outcomes? Given the nature of FDA regulation of devices, perhaps this could be done some time after market introduction, based upon real world evidence?

Answer 1. AdvaMed has prioritized strategies for assessing and promoting the value of medical technologies and diagnostic tests for a wide range of stakeholders, including patients, providers, payers and the overall health care system. To that end, we have developed a comprehensive approach, or framework, for assessing the value of devices and tests that takes into account not just the clinical impact of the device, but also non-clinical patient benefits, care delivery revenue and cost impact (such as improved efficiency), and the impact on society as a whole. Our framework is intended to drive that discussion of how to determine a medical technology's value and what evidence is appropriate to support that value assessment.

*Question 2.* Currently, FDA is trying to incorporate more real world evidence into its processes. Multiple GAO reports suggest Sentinel (for drug postmarket surveillance) data is poor quality—doesn't give us reliable information on outcomes.

Breakthrough drugs are approved based on early evidence of clinical superiority. This type of approval relies on quality postmarket data to validate the drug's early market entry. Is the FDA's inefficiency handling postmarket data hindering patient access to breakthrough drugs that can deliver substantial improvements in patient care? Could other sources of real world data buttress innovators' ability to validate their therapy's effectiveness?

Mr. Whitaker, we need to make available real world data to allow academia, pharma, payers to find the metric of value that is most appropriate, how will NEST (for devices) be any more useful? The EU is also moving toward a post-market focused approval process for devices. What lessons has industry learned from working with EU regulators to ensure we are collecting useful information with the NEST system?

Answer 2. We appreciate the question and agree with your point that quality of data is critical. As you note, FDA is exploring opportunities to incorporate real world evidence into its processes, including the device review and post-market surveillance processes. FDA has provided initial seed funding for the NEST Coordinating Center, or the National Evaluation System for health Technologies. The NEST is in its initial stage of development, and just recently hired an executive director. AdvaMed appreciates that the NEST Coordinating Council, which will provide strategic direction on the entity's operations, includes representatives from the medical device industry. We look forward to engaging in robust conversations at the NEST Coordinating Council, with Congress, and with other stakeholders to ensure that data collected by the NEST is of good quality and yields meaningful information for FDA, manufacturers, and other stakeholders.

### SENATOR BENNET

*Question.* I have been working with Senator Isakson on updating the medical device inspection process so FDA resources can be efficiently used to address and remediate safety concerns.

Can you identify other steps we can take to ensure the safety of medical devices once they are approved and on the market?

Answer. Thank you for your work on S. 404. We appreciate your leadership in bringing more transparency and predictability to the medical device inspections process. Your bill would ensure that patients are best served by FDA by instituting a more efficient inspections process that focuses FDA's resources on the greatest public health needs. This improvement to the medical device inspections process, coupled with FDA's already existing broad authorities in the post-market space, ensures that patients have timely access to safe and effective medical devices.

RESPONSE BY CYNTHIA BENS TO QUESTION OF SENATOR WHITEHOUSE

*Question.* Regulatory capture has been a concern within regulated industries since Woodrow Wilson. In the case of the FDA, industry is not only regulated by the agency, but is also its funder. According to the Congressional Research Service, when the prescription drug user fee agreement was first authorized, user fees funded 10 percent of the Human Drug Program's activities. In 2016, it was nearly 65 percent. The medical device user fees covered 16 percent of the device center's costs in 2006, compared with 35 percent in 2015.

As the size of the user fee agreements grows to support an increasing percentage of the FDA's review activities, what are the warning signs Congress should look for as evidence of possible regulatory capture?

Answer. Senator Whitehouse, thank you for your question and your concern about the potential for regulatory capture at the Food and Drug Administration (FDA). As a non-profit organization dedicated to improving the health and well-being of older Americans, the Alliance for Aging Research has consistently advocated for levels of funding that allow the FDA to carry out its mission while emphasizing the need to strike a balance between appropriations and user fees.

As you stated, user fees support more than half of human drug review activities and over one-third of device review activities at the FDA. While these are significant portions of the FDA's budget, the agency has capably carried out non-user fee-funded activities in a timely manner and responded to public health emergencies when they occurred. Congress should remain attentive to funding imbalances that could render the agency incapable of filling positions supporting non-user fee-funded activities or lead to an overemphasis on aggressively meeting medical product review times at the expense of other regulatory initiatives.

If future user fee reauthorizations continue on their current trajectory and the FDA also receives stable increases in appropriated funding for activities outside the scope of the negotiated agreements, I do not believe regulatory capture is imminent. However, if the FDA does not receive steady increases in budget authority and proposals like the fiscal year 2018 Trump Administration Budget Blueprint are adopted, I fear the pendulum could swing in the opposite direction.

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

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