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EXAMINING FDA'S PRESCRIPTION DRUG USER FEE PROGRAM

WEDNESDAY, MARCH 22, 2017

House of Representatives,

Subcommittee on Health,

Committee on Energy and Commerce

Washington, D.C.

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

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

Staff present: Adam Fromm, Director of Outreach and Coalitions; Jay Gulshen, Legislative Clerk, Health; Carly McWilliams, Professional Staff Member, Health; Alex Miller, Video

Production Aide and Press Assistant; Jennifer Sherman, Press Secretary; Danielle Steele, Policy Coordinator, Health; and John Stone, Senior Counsel, Health; Jeff Carroll, Minority Staff Director; Samantha Satchell, Minority Policy Analyst; Kimberlee Trzeciak, Minority Health Policy Advisor; and C. J. Young, Minority Press Secretary.

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

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

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

The committee has been reviewing the Prescription Drug User Fee Agreement since December when it was transmitted to Congress and publicly posted. As I stated in our hearing on the generic and biosimilar programs earlier this month, Chairman Walden and I are committed to shepherding the user fee legislation through committee following regular order and getting it to the House floor with ample time to spare. Reauthorization of the user

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

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

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

through which new treatments come to the bedside.

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

I am also encouraged that the Food and Drug Administration will dedicate resources to modernize clinical trials and evidence development including the utilization of real-world evidence in investment in biomarkers. Real-world evidence has the potential to increase sufficiency and foster robust data collection and analysis. Advancing development of biomarkers has significant promise to accelerate regulatory decision making and expedite the pace of clinical trials without sacrificing standards for efficacy and safety. Other provisions incorporated into the proposal for PDUFA VI -- okay, you made me say it -- PDUFA VI. I was trying to just call it the user fee agreements -- reflects the top priorities of this committee in the 21st Century Cures Act. Again I want to reiterate my commitment to ensuring that this reauthorization stays on track. We all know there are a lot

of competing influences this year, but this year will mark the fifth renewal by Congress, and it is widely agreed that the prescription drug user fee agreements will provide for the timely review of new drug and new biologic license applications. Again I want to underscore that is a good thing.

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

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

[The statement of Mr. Burgess follows:]

**********COMMITTEE INSERT 1**********

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

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

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

I was disappointed to see the line in the administration's testimony that they do not stand behind these agreements and hinted towards reopening the painstakingly negotiated products.

As we know, we are here today as the result of months of work between FDA and stakeholders to examine the program, figure out what is working and what can work better, and come to an agreement on how the program should be for the next 5 years through a public, drawn-out process.

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

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

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

The commitment letter for PDUFA VI includes a number of performance goals meant to help the agency with recruiting and retaining the scientific and professional staff needed to keep pace with the science. For the first time, PDUFA VI also includes specified agency hiring goals. This builds all the hiring provisions into the 21st Century Cures that will help the agency to compete with the private sector in terms of competitive salary, and gives the agency the authority to hire scientific and technical staff needed to support medical project review.

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

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

I want to thank the agency and the stakeholders for their

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

[The statement of Mr. Green follows:]

**********COMMITTEE INSERT 2**********

Mr. Guthrie. [Presiding.] The gentleman yields back his time.

Mr. Green. Do we have any other opening statements? No, okay.

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

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

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

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

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

Also, this program has allowed us to accommodate the advances in medical science that have occurred recently over the last several decades. Congress and the U.S. investment in NIH and in biomedical research has caused tremendous growth in scientific

understanding. Now we are really contemplating, we have approved drugs for example that are antisense oligonucleotides that act directly on people's DNA. We are looking at multiple applications for gene therapies although none have been approved yet. We are looking at multiple cellular therapies that are under development.

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

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

They want to know, they want to tell us how trials should be designed that work for patients. People always wonder why there is so many dropouts in the trials, missing data. Well, because we designed the trials in a way that patients couldn't participate. So the patient voice is critical, and then at the

end of the day how much risk are people willing to trade off in uncertainty for the benefits, the potential benefits of any given therapy. And this will require a rigorous process to generate and develop all these data and bring the patients in, in a rigorous way. It is envisioned in Cures and laid out in Cures, and the programmatic enhancements of PDUFA VI would bolster our ability to do that in a timely manner. Also, there is support for the Breakthrough Therapy Program. Now what I will say about that is that is probably the first program that has really shortened drug development. As we have all said, drug review isn't the problem. It occurs now in a timely manner, predictable manner, based on PDUFA. But drug development is still a very gnarly problem. It takes too long and it costs too much, right, and there are many failures.

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

There is also, as was envisioned in Cures, support for biomarker qualification also for the better use of surrogate

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

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

[The prepared statement of Janet Woodcock, M.D. follows:]

**********INSERT 3**********

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

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

Dr. Woodcock. Yes. The Oncology Center of Excellence is considered a joint venture by the three medical products centers, Center for Biologics, Center for Devices and Radiological Health, and Center for Drugs. And so we put this together jointly, it resides up in the office right above us. Dr. Richard Pazdur is the director of that office. And the procedures that we are running, they will review the clinical oncology, the medical oncology portion of any product that comes in with a medical oncology indication to any of the three centers. So they will do the medical part of that review, and Rick will direct it, but it will include oncologists from Drugs and Biologics as appropriate to that particular cancer area.

So we have worked out the procedures and so forth and we

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

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

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

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

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

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

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

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

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

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

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

information.

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

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

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

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

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

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

Dr. Woodcock. If there is not a reauthorization, we must initiate our reduction in force process where we would prepare

to let go of for the Center for Drugs is maybe 70 percent of the staff working on the process of review in new human drugs. And we do have carryover balance within the user fee agreements that we are supposed to hold some money back. In case the program terminates we can, over several months, have an orderly process to let go of the staff. And that we would have to start thinking about that in July because there are complicated personnel rules that have to do with who has to be notified first and so forth.

Mr. Green. Okay, thank you. There seems to be a misunderstanding about the drug development process. We hear often that new therapies take about 10 years to develop and some seem to think that means the application languishes at the agency for a decade. In fact, the FDA review is a final step in the development process and more efficient than ever. Can you explain to this committee how PDUFA VI builds on the past successes of the program and helps the agency work with stakeholders to not be a bottleneck but a strong partner in getting these new treatments to patients in need?

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

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

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

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

Many provisions of the user fee agreements resemble ideas we advanced in Cures, things like biomarker qualification programs, incorporation of the patient perspective in decision making, and the advancement of innovative clinical trials are goals we have shared. I am concerned about the impact that the

administration's proposed hiring freeze would have on FDA, and could it be made hard to advance these shared goals?

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

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

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

Mr. Green. Well, my time is almost up. And I know our goal

is to make sure you have the resources to do it quicker and not lay in another level of bureaucracy to make it even longer. Thank you, Mr. Chairman.

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

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

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

A question for you, Diana DeGette and I sent a letter a couple weeks ago to OMB asking about the federal hiring freeze that the President announced as it relates to the implementation of 21st

Century Cures. And of course as you know we came up with offsets, dollar for dollar matching to help with the half billion dollar increase that we gave for the FDA.

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

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

Dr. Woodcock. Well, I am not in a position to discuss that particularly, I can talk about what programmatic needs there will be. Clearly, the patient focused drug development is going to need different kind of scientists than we have traditionally had. We have had laboratory scientists who are looking in test tubes and doctors who are -- we are going to need social scientists and other folks who can actually talk to people and get rigorous

evidence about what their needs and preferences are and who can work on instruments, say, patient reported outcome measures and so forth. So that is one category that we don't necessarily have enough of.

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

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

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

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

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

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

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

Dr. Woodcock. Our analysis of the issues with generics is more that, you know, about ten percent of what we call reference drugs, the brand drugs, never get a generic filed to them. And so this seems to be a market phenomenon, competition is only

attracted where people think they can make money by competing, and the small source products and so forth.

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

So there, and we have agreed that we would set up a pre-program similar to kind of like the prescription drug user fee where before they send in the application we have meetings with them and we give them advice and we help them develop their products, so by the time they get the application in the door it actually could be approvable.

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

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

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

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

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

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

Mr. Schrader. Second question on the biomarkers. I think that is a great idea because it takes as you said, many times it takes awhile to get these drugs to market and many of them do fail. And so a lot of the manufacturers want to have some idea if they

are on the right track and you want to have some idea if they are on the right track, so early intervention and changing things would be appropriate.

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

Dr. Woodcock. We have a program known as Accelerated Approval. For some biomarkers such as blood pressure, their benefit is unequivocal and we don't need to keep proving over and over again that lowering blood pressure keeps you from getting strokes and so forth. We know that. But many other biomarkers are, quote, surrogate endpoints that we aren't a hundred percent sure that they are going to translate into benefit, and therefore we would give an accelerated approval it is called. That is kind of a misnomer, kind of misleading, but what that means is we are approving us based on the biomarker, but they have to do further studies. They are required to do further studies after approval to show that their drug actually causes clinical benefit.

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

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

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

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

Mr. Lance. Yes, Dr. Woodcock.

Dr. Woodcock. So, for example, real-world evidence, their guidance and so forth we would put out. 21st Century Cures has a broader qualification process, so it includes patient reported outcomes, clinical outcome assessment, as well as biomarkers,

whereas the PDUFA agreement is about biomarkers. However, we are going to put up the same process for everything, the Cures process, which puts in place timelines and obligations on both the submitters and the agency. So we will put that across the board.

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

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

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

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

Dr. Woodcock. Yes.

Mr. Lance. Is that the way it works?

Dr. Woodcock. Yes.

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

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

Mr. Lance. Thank you, Dr. Woodcock.

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

Mr. Guthrie. The gentleman yields back and Mr. Cardenas is recognized for 5 minutes for questions.

Mr. Cardenas. Okay. I will try to yield back a minute and 25 seconds or more to keep up with the program here. Thank you very much, Mr. Chairman, for holding this hearing. Dr. Woodcock, what is the significance of September 2017 as far as your professional world goes?

Dr. Woodcock. If these various user fee programs are not reauthorized at that time, we must initiate processes to let go

of the staff and wind down the program. There is money in all these agreements to do that. There is some money held back.

Mr. Cardenas. Yes, money held back to wind it down --

Dr. Woodcock. That is all.

Mr. Cardenas. -- which only expends over a few more months.

Dr. Woodcock. That is correct.

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

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

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

Dr. Woodcock. Well, what we would expect is the productivity would slow down as we approach the brink, tremendously. This has happened once before where we approached it and we lose staff. Our people are heavily recruited into other jobs and they aren't paid as we have all discussed, they aren't

paid as much as private sector. And so I would expect we would start to lose people very early who would leave before they got their notice.

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

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

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

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

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

Dr. Woodcock. I believe that is very accurate.

Mr. Cardenas. I mean, do our job legislatively by the September '17 deadline.

Dr. Woodcock. Yes.

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

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

Now that can be a very heavy decision say if it is a safety biomarker. We are saying we are trusting human lives to the

results of this biomarker. So there is a lot of scientific work that has to go in to make sure that biomarker is providing reliable information to make that decision.

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

Mr. Guthrie. Okay, thank you. The gentleman's time has expired.

Mr. Cardenas. Thank you, Chairman.

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

Mr. Long. Thank you, Mr. Chairman, and thank you, Dr. Woodcock, for being here today. I would like to spend my time with you discussing a very vulnerable population, one that I personally focused on helping. Every year, nearly 200,000 newborns in the United States are admitted to neonatal intensive care units for treatment. Due to the numerous challenges and despite current pediatric incentives, the last new drug for this population was approved in 1999. Last year my colleague on

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

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

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

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

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

So the first thing that had to be done was say what is the standard of care in the NICU, in the neonatal intensive care unit, and then you can say what are the biggest unmet medical needs for

neonates, and then you can start talking about, okay, do we have a trial network or do we have some type of infrastructure that could actually evaluate a new therapy were it developed? And they are working on doing that internationally which is really good news. So I would be happy to update you on the progress on that.

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

Dr. Woodcock. That is right.

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

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

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

And Mr. Chairman, I yield back.

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

Ms. Matsui. Thank you, Mr. Chairman.

Thank you, Dr. Woodcock, for being here. It is wonderful to have you here. First of all, I want to mention that I am concerned with the President's budget proposal and how it might impact the work that this committee is doing to reauthorize these vital agreements that they have. And I don't think it would be wise to renegotiate the user fee agreements that FDA and the industry have worked so hard to reach, nor do I think it would be wise to impose drastic cuts to the agency's budget authority that would endanger the FDA's ability to collect these user fees. FDA performs many critical functions to keep our food and drugs safe and we cannot afford to compromise that.

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

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

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

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

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

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

is not all about blood pressure meds and gigantic trials and heart disease, okay, it is about people who have the very rare diseases pose different problems in development.

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

Dr. Woodcock. Well, we were completely surprised after the Breakthrough provisions were passed that we got so many applications, all right, and so it has been extremely successful in getting designations. We are only supposed to designate drugs that preliminary data, their early data they develop in the clinic shows it may be a game changer in the disease. It really changes, may change the disease; it isn't proven yet.

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

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

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

Ms. Matsui. Right.

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

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

Mr. Guthrie. Thank you. The time has expired, and we

recognize Mr. Bilirakis for 5 minutes for questions.

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

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

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

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

as you know.

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

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

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

So even in advance of implementing these we have gotten sort of the basics down about how to do these reviews more effectively

given that we agree with you, this is the future of products. But the PDUFA program proposes that more resources be given to the Device Center to conduct these reviews of drug related, drug-led combination products of which many of these are.

Mr. Bilirakis. Okay, very good. I yield back, Mr. Chairman. Thank you.

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

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

Dr. Woodcock. Thank you.

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

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

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

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

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

Dr. Woodcock. I have to get back to you on specifics, are

there any. In general, the orphan diseases, the rare diseases are sort of throughout life. Many of them start in childhood and so children are usually studied.

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

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

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

Dr. Woodcock. Yes.

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

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

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

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

Dr. Woodcock. I do.

Ms. Eshoo. You live within a legal framework.

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

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

Thank you, Mr. Chairman.

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

Mrs. Blackburn. Thank you, Mr. Chairman.

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

As Chairman Upton mentioned, 21st Century Cures, the

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

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

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

Mrs. Blackburn. Just an expectation or timeline.

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

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

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

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

Dr. Woodcock. A final guidance for the generic?

Mrs. Blackburn. Yes.

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

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

Dr. Woodcock. Sure. You know, there are many things we are trying to do, one of them though is trying to incentivize development of drugs, new drugs that don't have these abuse liabilities to treat pain, and we have approved a number of them.

They are often for specific conditions.

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

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

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

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

Let me just begin by thanking you and, Dr. Woodcock, for coming back. You have been at that table many times and thank you so very much. Chairman Burgess who is not here today, but I want to thank him for holding this hearing on the Prescription Drug User Fee Agreement reauthorization. Since I came to Congress some 12 years ago back in '04, Congress has come together under the leadership of both Democrats and Republicans to pass

this important bipartisan legislation. Just last year we passed the 21st Century Cures Act that this committee drafted and passed unanimously to help boost the resources of the Food and Drug Administration and encourage the development of new treatments.

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

Through additional resources made possible by PDUFA V, the FDA has been able to work with industry to make available new treatments for rare diseases through the Breakthrough Therapy Program. Through November of last year, FDA has granted, I am told, 165 breakthrough therapy requests. This includes treatment in many areas that disproportionately impact my constituents and African Americans throughout the country.

Breakthrough designations have been granted for diseases like HIV and hepatitis C, and colorectal cancer, all of which impact minorities at high rates. PDUFA VI has the potential to make advancements in areas from breakthrough therapies and

real-world evidence to clinical trials and biomarkers. The additional resources made possible through the proposed new fee structure can help FDA build the workforce needed to complete these new tasks.

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

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

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

Dr. Woodcock. Not generally. The paradigm is changing and

typically over time treatments for cancer as well as other disorders have been according to disease. So in cancer it is what we call histology, which basically means the organ that the cancer originated in. That is why we call it colon cancer or we call it whatever cancer, lung cancer, right. But these molecular alterations may go across diseases and it may be only a small subset of each of these cancers are driven by the same molecular alteration. That isn't something that has really been looked at very closely in children. It may be that there are rare mutations in children that are the similar as the mutation in adult for these molecular targeted therapies.

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

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

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

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

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

Mr. Sarbanes. Thank you, Mr. Chairman.

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

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

And I was wondering if you would just talk a little bit about that topic. And obviously the agency is going to have to come up with, and I know you are in the process of doing this, a kind of formal process for identifying what qualifies as real-world evidence and then how it gets gathered and then how it gets translated back to the agency, how much weight is given to it as

part of the overall analysis that is done by the staff there at the FDA. So if you could maybe just talk about that a little bit more that would be helpful.

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

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

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

Mr. Sarbanes. Can you comment on how sort of off-label use

relates to that?

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

So what we are working with a large number of outside parties who are gathering this information up in different ways and then they want to collect that experience of the patients, those rare patients, and then perhaps if they responded and we can document that then maybe we can add that to the label and say if you have a rare patient like this come in they should be treated with this targeted therapy too. So that is an example.

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

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

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

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

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

So that I think is the kind of accumulating information. We

can't just have people sort of think great thoughts absent examples of what can be done.

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

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

Dr. Woodcock. Thank you.

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

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

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

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

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

STATEMENT OF JEFF ALLEN, PhD

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

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

the FDA approved them on average nearly 6 months faster.

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

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

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

The agreement will help create a process in which new tools can be accurately assessed and ensure their appropriate use.

PDUFA VI enhances the use of real-world evidence. Once a drug reaches real-world populations there may be unanswered questions about its effects, particularly in patients not represented in clinical trials. The collection of real-world evidence allows for a greater understanding of drugs currently in use. By allocating user fee funding toward these programs, the FDA and other stakeholders will be able to identify limitations and explore different opportunities for the use of data collected from post-market experience. To that end, FDA approved labels should be a vitally important source of information to guide the safe and effective use of prescription drugs. However, in some instances, such as drugs that have gone off patent, labels may have become outdated and no longer reflect optimal use. This is illustrated by extensive discrepancies between FDA approved labels and widely accepted practice guidelines.

The FDA could play a greater role in evaluating the relevant data to update the product label as appropriate and adjudicate between the uses backed by strong evidence and those backed by less persuasive information. This would establish a high standard for post-market evidence and make the product labels more useful. For the programs of this proposed user fee agreement to

succeed, the full budget of the FDA must be robust and the capacity of which the agency can maintain and hire the best scientific minds must be unencumbered.

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

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

[The prepared statement of Jeff Allen, PhD follows:]

**********INSERT 4**********

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

STATEMENT OF KAY HOLCOMBE

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

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

The success of PDUFA in bringing down the time of new drug review has led over the years to substantial expansion of the program in terms of the numbers and kinds of commitments FDA has made annually from increasing its efficiency in communicating with drug developers to enhancing its post-market surveillance and monitoring of drugs throughout their life cycles to applying best review practices across all review divisions to enhancing processes to review and approve therapies for rare diseases to

executing systematic approaches to measuring the benefit-risk ratio of potential drugs and to seeking and incorporating patient perspectives in that assessment.

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

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

The PDUFA VI goals, including expanding expertise in diverse statistical methods, piloting innovative clinical trial designs and computer modeling and simulation, use of biomarkers as surrogate endpoints, and more frequent and appropriate use of real-world evidence or big data will transform drug development.

All of these goals which attempt to bring 21st century science to the fore in this agreement will augment, not completely replace, tried and true methods of data collection. In the end, these new approaches will add to the old to make drug development more efficient while not compromising the statutory gold standard of substantial evidence of safety and effectiveness.

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

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

The majority of costs paid by user fees are for personnel.

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

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

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

Mr. Guthrie. Thank you.

Ms. Holcombe. -- for access to new medicines first.

[The prepared statement of Kay Holcombe follows:]

**********INSERT 5**********

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

STATEMENT OF ANNE PRITCHETT, PhD

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

For over 2 decades, PDUFA has helped to bring innovative medicines to patients by providing greater clarity and predictability in the science-based drug review process. Today, I just want to briefly share PhRMA's perspective on the PDUFA program and key elements of the PDUFA VI agreement. You know, first, I just want to note that we view user fees as an important mechanism to support the critical work of the FDA and human drug review process, and note as a result of this program over 1,500 new drugs and biologics have been approved since 1992. The number of new medicines being approved on their first review cycle is at a historic high, and as we heard earlier, the review times have dramatically dropped by more than half since the 1990s as a result of this agreement.

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

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

And I want to briefly touch on some key elements of the agreement. First, obviously PDUFA VI facilitates science-based

integration of the patient perspective into the development and regulatory review of innovative medicines. Over the course of PDUFA VI, FDA will be holding a number of workshops to gather stakeholder input to inform a range of guidances that are focused on how do we better incorporate the patient element into all stages of drug development and review.

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

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

Fourth, PDUFA ensures that the FDA will be able to hire and maintain a strong scientific medical and regulatory workforce to

advance its public health mission. For the first time, PDUFA VI includes detailed hiring goals and includes dedicated resources for the recruitment and retention of a world-class scientific workforce. And I would note it also includes independent outside consultants to help facilitate the agency in developing a comprehensive hiring strategy.

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

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

[The prepared statement of Anne Pritchett, PhD follows:]

**********INSERT 6**********

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

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

Mr. Green. No objection.

Mr. Guthrie. No objection, so ordered.

[The information follows:]

**********COMMITTEE INSERT 7**********

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

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

And what we found by comparing the FDA labels to practice guidelines that are constructed by medical oncologists is that the uses that are recommended by expert oncologists are usually far beyond that of what is contained in the FDA label. So the question is, should the product label have a role in the agency which we trust to evaluate medicines for them to get on the market,

should they have a more active role in looking at potential label modifications further down the life cycle of the drug to ensure it is supported by the highest quality evidence.

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

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

Mr. Guthrie. Yes.

Mr. Allen. I think it could --

Mr. Guthrie. When it needs to be.

Mr. Allen. The agency certainly does in terms of safety, but the same mechanisms aren't in place with regards to alternative uses. So one could imagine that perhaps it is worth having a longer discussion about the ability for over a certain period of time perhaps after the patent expires that there be some process for review of post-market evidence in order to make sure that the way the drug is being used is supported by the highest quality of evidence, so the people who are prescribing and using it are able to tell the difference between what is high quality and what is just an anecdotal use.

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

Mr. Allen. Yes. I think it is worth a longer conversation

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

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

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

Mr. Green. Thank you, Mr. Chairman.

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

the ultimate transmission of FDA PDUFA VI recommendations kicked off nearly 2 years ago in July of '15.

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

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

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

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

Ms. Holcombe. Well, we are getting faster.

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

Ms. Holcombe. Not that I am aware of.

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

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

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

Ms. Holcombe. Yes, we do.

Mr. Green. Okay. You note in your testimony that the drug development process, the most time-intensive part of bringing a drug to market, it is my understanding that on average it takes between 10 to 12 years to develop a drug. Recognizing this, we included in the 21st Century Cures a revision that would have FDA host a public workshop and issue guidance on innovative trials and designs and approaches. Would you please explain further how innovative trial designs may help your member companies in bringing treatments to market quicker and, in addition, would you discuss how PDUFA VI builds off of what Cures' effort to support the use of innovative drug trial designs?

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

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

evidence of safety and effectiveness that we all need to have and the answer to that is yes, we can.

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

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

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

The question I have is as we transition to new models to approve medicines we have been talking about that whether that is changes in clinical trials or other things, how do you see the legal environment evolving to allow this to happen? I will start with Dr. Pritchett. Because, I mean all of us are realists. We know, I mean, I was a medical doctor before, you know, as you transition to a new way to approve a product there is going to be people out there that are looking to throw a wrench into the

gears by saying it didn't prove what it was supposed to prove and that is why my particular client has been hurt. And so I mean there are legal ramifications of trying to do this also, any thoughts?

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

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

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

perspective, et cetera, but I think this is an important topic that we would welcome to have further discussion.

Mr. Bucshon. Okay, because I could see that the FDA and others very quickly retract their thoughts on these things as soon as we have some big class action lawsuit against the FDA and everybody else. So I am just, you know.

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

Mr. Bucshon. Okay, great, any other comments from the other panelists?

Ms. Holcombe. I think one of the important things to recognize about PDUFA VI is that in some respects takes account of this type of concern by initiating under PDUFA VI pilot programs, where the agency and the industry are going to work together to pilot these various trial designs or model-informed drug development approaches and determine whether in fact with input from outside stakeholders, whether these kinds of designs, this kind of way of developing drugs is going to produce the sort of good evidence, solid evidence that we need to make sure this product is safe and effective when it goes on the market.

Mr. Bucshon. Okay, anything else? Well, anyone, for all of you, can anyone give us a sense of how they envision the FDA

utilizing the authorities in 21st Century Cures Act in PDUFA VI, that the provisions involving the use of real-world, so-called real-world evidence to support their decision making how we would envision that being incorporated?

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

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

Mr. Guthrie. The gentleman yields back. Seeing no questions from this side, Ms. Brooks from Indiana is recognized

for 5 minutes for purpose of asking questions.

Mrs. Brooks. Thank you, Mr. Chairman.

Dr. Pritchett, PDUFA VI creates a significantly revised fee structure which replaces current levies on manufacturing facilities and on products. Can you -- and I appreciate -- short in time and I have a couple of other questions for others, can you explain this revised fee structure and how is it beneficial for all parties?

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

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

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

One thing was that it placed equal emphasis in terms of percentage of dollars collected on all three components, including the application fee which is the least predictable

source of revenue. There is very little perfect ability to predict the number of applications that are going to come into FDA on an annual basis. They have a lot of experience so they can give you a range, but if you collect 50 instead of 60 that makes a huge difference in the total revenue that you are collecting. So could we reduce the dependence on the application fee and increase the dependence on other fees? The second thing that was wrong was the manufacturing facility fee which is a nightmare to calculate mostly because drugs aren't just manufactured like I make mine in my facility and you make yours in your facility. Lots of people make drugs in the same facility, so figuring out whose was where when and how often and so forth. So could we offload that fee, could we calculate the rest of the fee based on number of products?

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

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

Ms. Holcombe. We called it a widget, okay.

Mrs. Brooks. Okay.

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

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

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

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

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

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

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

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

Mrs. Brooks. I yield back. Okay, thank you.

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

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

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

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

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

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

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

Ms. Holcombe. Yes.

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

to these patients.

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

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

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

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

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

Without objection, the subcommittee is adjourned.

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