

FDA USER FEE REAUTHORIZATION: ENSURING SAFE AND EFFECTIVE DRUGS AND BIOLOGICS

HYBRID HEARING

BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES
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²Legislation has been retained in committee files and also is available at <https://docs.house.gov/Committee/Calendar/ByEvent.aspx?EventID=114371>.

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HEARING ON; FDA USER FEE REAUTHORIZATION: ENSURING SAFE AND EFFECTIVE DRUGS AND BIOLOGICS

THURSDAY, FEBRUARY 3, 2022

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

The subcommittee met, pursuant to call, at 10:02 a.m., in the John D. Dingell Room 2123, Rayburn House Office Building and remotely via Cisco Webex online video conferencing, Hon. Anna G. Eshoo, (chairman of the subcommittee) presiding.

Members present: Representatives Eshoo, Butterfield, Matsui, Castor, Sarbanes, Welch, Schrader, Cárdenas, Ruiz, Dingell, Kuster, Kelly, Barragán, Blunt Rochester, Craig, Schrier, Trahan, Fletcher, Pallone (ex officio); Guthrie (subcommittee ranking member), Upton, Burgess, Griffith, Bilirakis, Long, Bucshon, Carter, Dunn, Curtis, Crenshaw, Joyce, and McMorris Rodgers (ex officio).

Also present: Representative Schakowsky.

Staff present: Elizabeth Ertel, Office Manager; Waverly Gordon, Deputy Staff Director and General Counsel; Tiffany Gutierrez, Staff Member; Stephen Holland, Health Counsel; Mackenzie Kuhl, Press Assistant; Una Lee, Chief Health Counsel; Meghan Mullon, Policy Analyst; Kaitlyn Peel, Digital Director; Caroline Rinker, Press Assistant; Chloe Rodriguez, Clerk; Kylea Rogers, Staff Assistant; Andrew Souvall, Director of Communications, Outreach and Member Services; Kimberlee Trzeciak, Chief Health Advisor; Asad Ramzanali, Legislative Director; and Vincent Amatrudo, FDA Detailee; Sarah Burke, Minority Deputy Staff Director; Grace Graham, Minority Chief Counsel, Health; Nat Hodson, Minority Staff Director; Peter Kielty, Minority General Counsel; Emily King, Minority member Services Director; Clare Paoletta, Minority Policy Analyst, Health; Kristin Seum, Minority Counsel, Health; Kristen Shatynski, Minority Professional Staff Member, Health; Olivia Shields, Minority Communications Director; Michael Taggart, Minority Policy Director.

Ms. ESHOO. Good morning, colleagues. The Subcommittee on Health will now come to order.

Due to COVID-19, today's hearing is being held remotely as well as in person. For members and witnesses taking part in person, we are following the guidance of the CDC and the Office of the Attending Physician. So please wear a mask when you are not speaking.

For members and witnesses taking part remotely, microphones will be set on mute to eliminate background noise. Members and witnesses, you will need to unmute your microphone when you wish to speak.

Since members are participating from different locations at today's hearing, recognition for members for questions will be in the order of subcommittee seniority.

Documents for the record should be sent to Meghan Mullon at the email address we have provided to your staffs, and all documents will be entered into the record at the conclusion of the hearing.

OPENING STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

The Chair now recognizes herself for 5 minutes for an opening statement.

Our Health Subcommittee today is holding its first hearing on the FDA Medical Product User Fee Programs, each of which must be reauthorized every five years.

The current User Fee Programs need to be reauthorized by September 30th of this year, and the focus of today's hearing will center on reauthorizing three of the four User Fee Programs for fiscal years 2023 through 2027, prescription drugs, generic drugs, and biosimilars.

The creation of the Prescription Drug User Fee Act, or PDUFA, in 1992 came at a time in our country when HIV and AIDS had reached epidemic proportions. In the late 1980s, Americans with HIV, AIDS, and cancer had to wait years for lifesaving medicines to work their way through the notoriously backlogged approval process at the FDA.

Thousands of patients were dying yearly because the agency simply did not have the resources nor the staff to review human drug applications.

PDUFA introduced a new opportunity for the FDA to take a transformative approach and vastly expedite its drug review process.

By authorizing the collection of user fees from industry, PDUFA provided the FDA with an additional revenue source to hire more staff and meet ambitious review deadlines for new medicines to treat the deadliest of diseases.

Prior to PDUFA the average review time for standard new drug applications and biologics' license applications was 29 months. Today, PDUFA's timeline for standard review is ten months, and the timeline for priority review is only six months.

Following the success of the PDUFA Program, Congress enacted the Generic Drug User Fee Act, or GDUFA, and the Biosimilar User Fee Acts, or BsUFA. I do not know quite how to pronounce that abbreviation. That was in 2012, to clear additional backlogs and ensure patients have timely access to safe and effective generic drugs and biosimilars.

These user fee agreements have successfully led to the development of more lifesaving products at reduced cost for the American people.

The user fees of each of these programs are strictly used to accelerate the FDA's drug and biologics review processes, and they supplement but do not supplement congressional appropriations to the FDA.

Every five years Congress reassesses the User Fee Programs to ensure that each program has a fresh chance to improve its goals of getting critical medicines to patients who need them.

Improvements to these programs are made with input from industry, regulators, and patient advocates while working in agreement with the FDA to ensure the agency is appropriately equipped to assess the next wave of diagnostics, vaccines, and therapeutics.

Today we are going to hear from representatives from the FDA, industry, and public health who have worked, I know, very hard together on negotiations for the User Fee Programs.

I am pleased that the parties have reached an agreement on the three that we are taking up today and the negotiated recommendations for each of these programs actually builds upon the successes of the existing programs and refined elements in light of the pandemic.

With these new programs, the FDA estimates that user fees for PDUFA will average \$1.4 billion per year. That is a hefty amount of money.

The user fees for GDUFA will average over \$600 million per year, and the user fees for the biologics program will average \$51 million per year.

So as we discuss the sixth reauthorization of PDUFA and the third of the other two, it is my hope that Congress will act quickly to reauthorize these User Fee Programs to ensure that companies can continue to innovate and FDA can quickly assess the next wave of lifesaving medications.

[The prepared statement of Ms. Eshoo follows:]

PREPARED STATEMENT OF HON. ANNA ESHOO

Committee on Energy and Commerce

Opening Statement as Prepared for Delivery
Of

Subcommittee on Health Chairwoman Anna G. Eshoo

Hearing on “FDA User Fee Reauthorization: Ensuring Safe and Effective Medical Devices”

March 30, 2022

Every day Americans rely on safe and effective medical devices. From the joy of an ultrasound during pregnancy to the distress of a cancer diagnosis via MRI, medical devices treat, diagnose, and monitor the health of patients.

When I was working on the original legislation that created the Medical Device User Fee Agreement process in 2002, we couldn’t imagine the innovative devices that are on the market today. And, without the user fees supplementing the FDA for the past 20 years, many of these innovations would be stuck in a backlog instead of helping patients.

A few months ago, I visited El Camino Hospital in my district, which is using radiation technology with AI to individually target tumors. This is just one example of the hundreds of devices that the FDA has approved or authorized since MDUFA was last reauthorized in 2017.

With this impressive innovation comes an increasingly complex FDA review process. Over the past 20 years, the User Fee Agreements have evolved to make sure that the FDA has the resources necessary so that its reviews are timely, transparent, and predictable.

MDUFA V is the latest evolution. The recently announced draft agreement provides FDA \$1.78 billion over five years in user fees. This is about ten times the amount provided in the original 2002 user fee agreement.

With this funding, the FDA’s Center for Devices and Radiological Health will be able to hire 387 new full-time employees while also meeting rising payroll costs.

The user fees will also fund successful FDA policies, such as the use of real-world evidence, the harmonization of international medical device regulatory activities, and patient engagement to inform the evaluation of products.

While MDUFA V is a significant increase in user fees from medical device makers, it’s important to keep in mind that user fees cannot and should not relieve Congress from its responsibility to fund the FDA in a robust way. That’s why I was pleased to see President Biden’s budget included a \$95 million increase for FDA’s medical product safety work.

Today, we will hear from representatives from the FDA, private industry, and public health about the negotiated medical device user fee agreement. As the mother of MDUFA, I look

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forward to shepherding this agreement through a swift reauthorization before the program expires on September 30th.

Ms. ESHOO. With that, the Chair now recognizes our wonderful ranking member, Mr. Guthrie, for 5 minutes for his opening statement.

OPENING STATEMENT OF HON. BRETT GUTHRIE, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH STATE OF KENTUCKY

Mr. GUTHRIE. Thank you, Madam Chair, and thanks to our witnesses for being here with us today.

Today marks the last stretch of a more than two-year process to reauthorize the four critical FDA user fee agreements that are foundational building blocks for medical innovation in the United States. These agreements ensure safe and effective lifesaving treatments and devices are approved and eventually reach patients.

We are here today to examine three of these four programs, PDUFA, the Prescription Drug User Fee Act; GDUFA, the Generic Drug User Fee Amendments—and I am going to go with the BsUFA—BsUFA, the Biosimilar User Fee Act.

The U.S. Food and Drug Administration, or the FDA, industry and other key stakeholders have been meeting regularly since 2020 to identify barriers to bringing drugs to market.

Although we will not be discussing medical devices today, I look forward to discussing the Medical Device User Fee Act with industry and FDA before this committee once an agreement is reached.

Congress originally passed PDUFA in 1992 to address significant delays in the drug review process at the FDA. The law authorized FDA to collect from companies who were submitting drug applications.

These fees helped ensure a timely review of drug applications by the FDA drug reviewers. As a result of the early successes of PDUFA, Congress in 2002 passed the Medical Device User Fee Act, and 2012 passed the Generic Drug User Fee Amendments and the Biosimilar Drug Fee Act to enhance competition in other parts of the life science industry.

These must pass agreements are reauthorized by Congress every five years on a strong bipartisan basis. For example, the FDA Reauthorization Act of 2017 passed under suspension in the House and by a 94-to-one vote in the Senate.

Since Congress established the first User Fee Program three decades ago, the FDA has approved over 1,700 drugs. By approving more drugs and generic options, Americans have more options and more affordable lifesaving medications.

User fees have also given the United States pharmaceutical industry a competitive advantage globally. In 2021, 38 out of 50 novel drugs approved globally in 2021 were first approved in the United States.

Another success of these programs has been the ability to bring more generic biosimilars to market, providing lower cost options for patients. In the first five years after the authorization of generic or the GDUFA in 2012, the FDA reviewed 98 percent of abbreviated new drug applications, or generic drug application, that had been backlogged.

Further, since reauthorizing the Biosimilar or BsUFA the same year, the U.S. healthcare system is modeled to save \$100 billion in

analyzed savings resulting from increased marketplace competition due to the availability of FDA approved biosimilars over the next five years, according to a report by—and I will spell this one out—IQVIA.

Since passage of 2017 FDA Reauthorization Act, which reauthorized all four user fee agreements, members of this committee have been building on a policy this bipartisan legislation established.

For example, Mr. Schrader and I introduced the Protecting Access to Safe Protective Medicines Act, and it was signed into law last year. This law helps increase competition in the marketplace by taking a technical clarification to the drug application process to prevent drug companies from gaming the system for more market exclusivity and in some case eliminating generics from coming to the market sooner.

I look forward to finding more opportunities to create bipartisan solutions to bring more drugs to the marketplace as quickly and safely as possible.

And looking ahead to the next few months, this committee will have a unique opportunity to help shape the drug and medical device approval process for years to come. Members will be given a chance to raise questions directly with industry leaders and regulators about past reauthorization agreements or specific policy priorities designed to increase innovation.

A top priority for me will be to ensure the FDA approved drugs or devices receive coverage by both public and private insurers as quickly as possible. This will be possible by allowing drug or device companies to share real time economic and clinical data with payers which will allow payers to plan ahead for formulary placement.

This policy ensures patients would receive timely access to new and novel treatments once approved by the FDA. Timely coverage of a drug will not only address critical care gaps, but will also further incentivize innovation.

Above all, I can underscore how critical it is for this committee and for Congress to reauthorize these agreements before September 30th. Doing so is imperative for patients to have access to life-saving treatments.

I thank you for the time, and I yield back.

[The prepared statement of Mr. Guthrie follows:]

PREPARED STATEMENT OF HON. BRETT GUTHRIE

**Opening Statement for the Honorable Brett Guthrie
“FDA User Fee Reauthorization: Ensuring Safe and Effective Medical
Devices”**

March 30, 2022

As Prepared for Delivery

Thank you, Madam Chair, for holding this important hearing.

Today we are building off the work we’ve done over the past several weeks to find additional opportunities to foster American biopharmaceutical innovation. The focus of today’s hearing is to discuss the recently announced Medical Device User Fee Amendments (ma-dew-fa). This will be critical to continuing to enhance our medical device ecosystem here in the United States.

Like the prescription drug industry, innovators working to develop new and innovative medical technologies experienced significant delays in getting their products reviewed by Food and Drug Administration experts. That is why Congress, regulators, and industry all came together to develop a solution in the Medical Device User Fee and Modernization Act of 2002 that would streamline the review process and help get these devices to patients more quickly. This agreement has since been reauthorized by Congress every five years.

The original MDUFA Act gave the FDA the necessary tools to hire more clinical experts to review device applications. It also offered industry the assurance of being able to hold the FDA to higher performance standards. The successes of

this partnership are clear as the FDA's Center for Devices and Radiological Health (CDRH) has granted novel technologies four times as many approvals, marketing authorizations and clearances over the past decade, largely resulting from policies made possible by past MDUFA authorizations.

The agreement before us today represents an ambitious agenda set by industry and CDRH experts. The goal is to ensure the FDA is doing everything it can to protect patient safety, while also supporting the development of medical device technologies.

Highlights include authorizing the FDA to collect \$1.78 billion from industry and potentially up to \$1.9 billion over the next five years to bolster CDRH's workforce to help get products reviewed and approved as quickly and as safely as possible. Of note, is the creation of the new Total Lifecycle Advisory Program, which CDRH states will help promote the long-term sustainability of the Breakthrough Device Program.

I was proud to support the creation of the Breakthrough Devices Program that was created as a part of the bipartisan 21st Century Cures Act. In 2021, CDRH granted breakthrough designation to 213 devices, and there have been over 600 designations made since the program's inception. This includes a device that

harnesses machine learning to help health care providers diagnose autism spectrum disorder.

However, I am still frustrated by the Biden Administration's actions to undermine the bipartisan supported Trump-era Medical Coverage of Innovation Technologies rule that would have helped to get breakthrough devices to seniors once a breakthrough device was approved by the FDA. This directly conflicts with earnest efforts made by Congress, CDRH, and the medical device industry to encourage investments in these emerging technologies. I encourage CMS to work to reverse this decision and work with the industry as well as their FDA partners to address outstanding concerns.

To that end, I am also continuing to push for the codification of the 2018 FDA guidance that permits pre-approval information exchanges between product sponsors and payors. These information exchanges help get products covered more quickly once they are approved by the FDA. My bill, the Pre-approval Information Exchange Act, would do just this and help public and private payors to make coverage determinations earlier based off real-time health care economic information exchanged between entities.

Additionally, offering needed clarity around the FDA's 2016 guidance on emerging signals is another important priority of mine in the device policy space,

and I am working on a solution to offer needed regulatory certainty on this issue. Outlining a process that affords companies the chance to work with regulators on addressing reported adverse health events associated with their devices will not only protect patients, but also create regulatory predictability that will protect against gaps in care for patients who rely on these devices.

I look forward to working with my colleagues over the next several months to reauthorize this important user fee agreement that will promote even greater innovation for decades to come. Thank you, and I yield back.

Ms. ESHOO. The gentleman yields back. A wonderful and important opening statement.

The Chair is now pleased to recognize the chairman of the full committee, Mr. Pallone, for his 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairwoman Eshoo.

Today the Health Subcommittee is beginning the critical process of reauthorizing the FDA's User Fee Program for prescription drugs, generic drugs, and biosimilars.

We will also discuss FDA's agreements with industry stakeholders on improvements to the review and development of important medicines.

The fees collected from these programs support the timely review of drug applications and other activities needed to support drug development, and as such, these programs are essential to FDA's mission to ensure that the agency has the resources and personnel it needs to review and approve safe and effective medical treatments in a timely fashion.

The current user fee authorizations expire later this year on September 30th, and it is critical that we pass these reauthorizations well ahead of the deadline so that FDA can continue its operations without interruption.

Over the past two years as we have confronted the COVID-19 pandemic, the American people have witnessed the important work the FDA does every day. The agency has led the critical review process and supported the development of lifesaving vaccines that are essential to our efforts to once and for all end this terrible virus.

The FDA has also reviewed and approved important therapies that are helping people fight the virus, and it has also helped to respond to medical supply chain issues that have led to shortages of some medical products.

The unprecedented nature of the pandemic has stretched FDA to its limit over the last two years, and the entire FDA workforce should be commended for their outstanding work not only in responding to this pandemic, but also for continuing to do all the other important work they are charged to do.

As we continue to face the COVID-19 pandemic, we simply cannot put FDA's funding in jeopardy, and that is why we must act expeditiously to reauthorize these important user fees.

It is also why Ranking Member Rodgers and I, along with our counterparts on the Senate Health Committee, sent a letter last week to Acting Commissioner Woodcock expressing concern that the FDA and industry have not yet reached agreement on the Medical Device User Fee Program.

This is troubling because we are now more than two weeks past the statutory deadline for Congress to receive the agreement, and this deadline is set by law. It is not a mere suggestion.

It is in everyone's interest for FDA and industry to reach an agreement, and I look forward to receiving a status update soon.

The proposed legislation and performance goals of the drug programs before us today show the progress and improvements that can be made with these user fee agreements. The performance goals include new policies that will help increase the consistency, efficiency, and effectiveness of drug reviews.

The proposed legislation strengthens staff capacity for the review of cell and gene therapies; improves review timelines for complex generic products; and develops the more competitive biosimilar markets.

So it is my hope that these proposals from FDA will lead to a more efficient and effective review of drugs and biosimilars while maintaining the agency's highest standards for safety and efficacy.

The focus on safe and effective development should ultimately provide for a greater number of approvals of lifesaving drugs and improved competition in a way that will help lower costs for our healthcare system and the American people.

And, Madam Chair, if I just may ask for a moment of privilege and address the subcommittee on a different topic.

For those of you who have not yet heard, Kim Trzeciak, the subcommittee's Chief Public Health Advisor, will be departing after nearly seven years on my staff. Kim was one of the first hires when I became the Democratic leader of the committee in 2015, handling the FDA portfolio first and then being promoted to lead the public health team in the majority, and she has shined throughout.

This committee and Congress have taken so much action over the last seven years in the public health space and Kim's fingerprints are on each of these laws.

She has been a trusted member of my team who has dedicated her career to public health, and I am incredibly grateful to her for her service to our country and for her counsel over the years, and I wish her nothing but the best.

And with that, Madam Chair, I yield back.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE JR.

Committee on Energy and Commerce

Opening Statement as Prepared for Delivery
Of
Chairman Frank Pallone, Jr.

Hearing on “FDA User Fee Reauthorization: Ensuring Safe and Effective Medical Devices”

March 30, 2022

Today we are continuing our work to reauthorize the Food and Drug Administration (FDA) user fees, which provide critical resources for the agency’s medical product review programs. All of the user fees expire on September 30th of this year, and Congress must pass these reauthorizations well ahead of that deadline to ensure FDA can continue to operate without interruption.

At today’s hearing, we will review the Medical Device User Fee Program, also known as MDUFA. Throughout the COVID-19 pandemic, the FDA’s Center for Devices and Radiological Health, or CDRH, has been at the forefront of regulating and adapting guidance to help develop and authorize diagnostic tests. It has also managed the supply chain for critical items like gloves, masks, respirators, swabs, and ventilators. The staff at CDRH have been working day and night to stay ahead of the virus, and they deserve our recognition and appreciation. Their work over the last two years has underscored the importance of ensuring that FDA resources are in place to make sure we have a safe and effective medical device supply chain. The draft agreement that we are discussing today between FDA and industry will substantially increase funds for CDRH, which will lead to a significant increase in staff capacity at the agency.

The performance goals included in the draft agreement will also allow for innovation through the creation of the Total Product Life Cycle Advisory Program Pilot, or the TAP Pilot. This pilot program will allow for earlier interaction between FDA and developers and will facilitate regular engagement throughout the medical device review cycle. This will hopefully lead to a sustainable program that builds safety and efficacy discussions into the front end of development, to speed innovation in a responsible way.

The draft also lays out new transparency measures that will ensure funds are being spent efficiently and going to the programs authorized by the agreement and the legislation we pass.

When I mention transparency, I want to also note the importance of the process we are undertaking here in the Committee today, and the process Congress has laid out for FDA and industry to reach the agreement we are now reviewing. By statute, as part of the MDUFA reauthorization, FDA is mandated to consult with regulated industry, patient and consumer representatives, and health care professionals, receive public comment, and submit recommendations to Congress no later than January 15th of this year.

This deadline is not a mere suggestion, it is law, and the process is important because it allows for FDA, industry, and members of the public to examine what has worked well, and

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where review programs can be improved through the reauthorization process. It also provides Congress with sufficient time to thoroughly review these recommendations and reauthorize the program ahead of the funding deadline.

FDA released its draft commitment letter to the Committee last Tuesday, more than two months after the January 15 deadline. FDA has not received public comment on the draft yet. This is troubling considering there are serious questions about numerous issues including how the agency and industry contemplated the extensions of programs due to sunset in their agreement.

There is still much to review and more work to be done, and we must act quickly. Failure to reauthorize the program on time would be catastrophic for patients relying on safe and effective medical devices.

While FDA and industry missed their deadline, this Committee will not. I appreciate FDA and industry being here today to help us understand their proposal. I also think it is important for us to discuss how we can improve the process, so this does not happen again in the future.

We will also review two other commonsense proposals. One bill, from Representative Schrier, would create a new advisory panel at FDA to bring an independent public health focus to regulatory decisions involving diagnostic tests, the importance of which we are still seeing during the COVID-19 pandemic. Another bill, from Representative Burgess, would incorporate cybersecurity into medical device applications, which is critical as medical devices become more interconnected and technologically advanced.

I look forward to the discussion today.

Ms. ESHOO. I often say we really are nothing without great staff. So, Kim, we are all grateful to you for the incredible work that has taken place and your leadership in working with both sides of the aisle over all of these years.

I am sure it has been a rich experience for you, but you have made it even richer for all of us. So God bless you on your continuing journey.

Did you say where she is going?

Mr. PALLONE. She is going to the FDA.

Ms. ESHOO. She is going to the FDA. How is that?

Do not forget us. Always remember your roots in this family. So I guess we will look forward to seeing you on the other side of the dais.

But thank you and bravo.

The Chair now is pleased to recognize the ranking member of the full committee, Represent Cathy McMorris Rodgers, for her opening statement.

And, Cathy, remember to unmute.

Mrs. MCMORRIS RODGERS. All right.

Ms. ESHOO. There you are. I am looking at the screen. I did not see you come in.

Mrs. MCMORRIS RODGERS. Madam Chair, yes.

Ms. ESHOO. That is great. It is great to see you.

Mrs. MCMORRIS RODGERS. And I agree. Kim, do not forget us when you get over at the FDA.

Thank you, Madam Chair.

**OPENING STATEMENT OF HON. CATHY MCMORRIS RODGERS,
A REPRESENTATIVE IN CONGRESS FROM THE STATE OF
WASHINGTON**

Today we are discussing the critical task of reauthorizing several key FDA User Fee Programs.

Thank you to the FDA and industry for submitting these agreements, these three agreements, before January's deadline and for your engagement over the last year.

These programs are designed to innovate as fast as possible while maintaining the FDA's gold standard of safety.

The goal is to provide FDA with the resources necessary to conduct timely and efficient reviews of human medical products, investing cutting edge technologies, and hire and retain agency experts to carry out these tasks.

These recommendations reflect a shared commitment to America leading the world in medical innovation, spurring competition, and ensuring timely access to safe and effective drugs.

The committee is in the process of reviewing the proposed agreements for the three User Fee Programs before us today. These agreements include provisions that will support emerging areas of drug discovery and streamlining the review and approval of treatment for rare diseases.

The PDUFA agreement also directs significant investments for the development, review, and approval of gene and cell therapy products.

The next five years can be game-changing with one-time curative therapies for diseases such as hemophilia, sickle cell, and rare pe-

diatric diseases. That innovation means hope for patients and their families, as well as lower overall healthcare costs required to treat those diseases today.

The new Star Pilot Program also proposed in PDUFA will expedite the delivery of promising therapeutics for diseases with unmet clinic needs.

I look forward to hearing from our witnesses on how PDUFA and GDUFA—that is what I was told—will bring competition to the market, increasing options and lowering cost for patients.

Competition, not price controls, has demonstrated the ability to lower drug prices, and these agreements are key to bringing more lower cost generics and biosimilar drugs to market. I am pleased to see proposals in both packages that will enhance approval of these complex generics and interchangeable products.

Over the course of the negotiation process we have heard from FDA, industry, and stakeholders on how the COVID-19 pandemic has impacted new treatments and cures to the American people. FDA gave rolling reviews to expedite the review of treatments and vaccines while not lowering the bar on safety.

Can FDA continue those process improvements for other diseases?

I also want to discuss today how the FDA is planning for an orderly transition from emergency use authorizations to full approvals and how we can get back to normal.

We clearly have more supply of vaccines than demand. So why do we not transition to routine distribution?

Rumor is that the Biden administration may ask for more COVID-19 funding, and I want to know how long the administration plans to be the sole purchaser of COVID-19 vaccines in the country.

At some point, and I hope it can be soon, the public health emergency will end. When that happens, American patients need to continue to have access to necessary vaccines, and we need to improve access to tests and treatment.

FDA plays a large role in that transition, and I want to learn more about what that takes and how these agreements will play a role.

FDA also works with companies designing critical trials for approval, including a number of treatments for Alzheimer's disease. I was shocked to find out that at the CMS proposed national coverage determination severely restricts Medicare coverage for a whole class of Alzheimer's treatments, including the recently FDA-approved Aduhelm, to only cover these drugs in CMS-approved clinical trials.

It also excludes those with Down's Syndrome from participating in covered trials, even though Alzheimer's may affect greater than 90 percent of those with Down's Syndrome over the age of 60.

This is wrong. We need clinical trials that more closely reflect the diversity of Americans, including those with disabilities.

Further, just because they may be excluded from trials today, it should also not hurt their access to FDA-approved drugs if their doctor determines it is the best decision for their health.

We are committed to moving these User Fee Agreements through Congress on time and through regular order. Now more than ever

let's work together in a bipartisan way to promote innovation, to lower cost with more competition, and deliver safe and effective drugs to Americans.

Thank you, and I yield back.

[The prepared statement of Mrs. McMorris Rodgers follows:]

PREPARED STATEMENT OF HON. CATHY McMORRIS RODGERS

Cathy McMorris Rodgers
House Energy and Commerce Committee
Subcommittee on Health
“FDA User Fee Reauthorization: Ensuring Safe and Effective Medical Devices”
March 30, 2022
As Prepared for Delivery

Thank you, Madam Chair....

INTRO

Today this Subcommittee will hold its third hearing to consider the reauthorization of the FDA user fee programs.

Congress has acted to authorize the Medical Device User Fee Amendments, or MDUFA (ma-doof-ah), four times before... and we remain committed to renewing this authority on time and through regular order.

I'd like to thank our witnesses for testifying today, and would also like to welcome back Dr. Shuren.

Dr. Shuren came before this Subcommittee when we last reauthorized these programs in 2017.

LATE SUBMISSION

Before we discuss the proposed agreements and the two bills for today's hearing, I'd like to express my disappointment with the failure of FDA and regulated industry to deliver their proposed agreement to Congress by the January 15 statutory deadline.

MDUFA negotiations have been ongoing for over a year, and we've had just **one week** to review the proposed amendment language and commitment letter before this hearing.

This delay hinders Congress's oversight responsibilities.

Reauthorizing these programs on time is a goal shared by all of us on this Committee and failure to do so will result in delayed patient access to needed medical technologies.

Further, I have raised serious concerns about a lack of transparency throughout this process.

In November, I wrote to then Acting Commissioner Woodcock about the delay in posting meeting minutes from FDA-industry negotiations.

To ensure transparency and progress... documentation of meeting outcomes and action items are supposed to be made part of the official record and made publicly available.

While this posting minutes publicly usually takes no more than 2 to 3 weeks...

...., during MDUFA Five negotiations, we saw delays of more than six months.

Even today, there are no meeting minutes posted for any meetings that took place after June 30, 2021.

I know that my colleagues and I are looking forward to getting answers today on what took so long for the proposed agreement to be delivered to our Committee...

....and how we can improve this process going forward.

Proposed Enhancements

Now, regarding the proposed MDUFA Five agreement...

...as well as two pieces of legislation – introduced by Representatives Burgess and Schrier.

Dr. Burgess's bill ensures the cybersecurity of devices is approved or cleared by FDA.

Dr. Schrier's advises on the real-world impact of medical device diagnostics.

We want to make sure FDA has the resources to keep up with cutting edge medical technology, such as artificial intelligence, robotic prosthetics...

.... and facilitate innovation and production of the more routine devices we rely on – syringes, gloves, gowns.

We need to make sure those resources are used wisely and improve people's quality of life.

The promise of American innovation will allow medical technology to help keep patients healthier, enable treatment at or close to home, and improve timely diagnosis and treatment.

This reauthorization requires FDA to leverage digital health technologies and real-world evidence in the review and clearance or approval of medical devices where appropriate.

The proposed enhancements also direct significant investment in hiring and retaining world-class scientific and technical staff.

There is no question that the COVID-19 pandemic severely disrupted business as usual for FDA to review applications and make timely decisions.

The Center for Devices and Radiological Health has especially had a daunting task.

FDA has fallen behind on the accountability part of the deal, missing 3 review goals during FY2020 and 6 during FY2021, according to Dr. Shuren's testimony.

I hope that FDA will improve going forward and that the hiring commitments and performance goals agreed to under MDUFA Five will get FDA back on track.

I am also encouraged that the commitment letter contains enhancements to improve performance accountability and financial transparency.

FDA has committed to publishing an annual 5-year financial plan, which will include hiring targets and a full accounting of where user fee funds are being spent.

MDUFA Five will also continue enhancing its Patient Science and Engagement program, which will prioritize including the voice of patients in the review process.

The goal of these improvements will improve pre-submission communication with innovators, make sure patients are heard,

.... and, overall improve the efficiency, integrity, and effectiveness of medical device reviews.

CONCLUSION

Reauthorizing MDUFA before September's deadline will allow agency operations to continue ...

...and will also ensure patients benefit from our biomedical innovation and advancements in medical technology.

This is a goal I believe is shared by each of my colleagues, and I look forward to today's discussion.

I yield back.

Ms. ESHOO. The gentlewoman yields back.

I now would like to introduce our witnesses for our first panel. I would say two stars from the FDA.

The first, Dr. Patrizia Cavazzoni. She is the Director of the Center for Drug Evaluation and Research at the FDA. She has testified many times before our subcommittee, and we welcome her here today and thank her for the work, the ongoing work which has been an extraordinary workload given the pandemic.

And Dr. Peter Marks, who is the Director of the Center for Biologics Evaluation and Research at the FDA.

We welcome you. We thank you for your leadership and work that you are doing, as I said, the really heavy load that has fallen on the FDA during the pandemic. Your service to the American people is nothing sort of extraordinary.

So thank you, again, for joining us today. We look forward to your testimony. I think you are familiar with our system of lights: 5 minutes for each.

Dr. Cavazzoni, you are recognized for 5 minutes .

STATEMENT OF PATRIZIA CAVAZZONI, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION; AND PETER MARKS, M.D., Ph.D., DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

STATEMENT OF PATRIZIA CAVAZZONI, M.D.

Dr. CAVAZZONI. Madam Chair, Ranking Member Guthrie, and members of the subcommittee, I am Dr. Patrizia Cavazzoni, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration.

I appreciate the opportunity to appear before you today, along with my colleague, Dr. Marks, to discuss reauthorization of the User Fee Program covering brand name drugs, generic drugs, and biosimilars.

We appreciate the efforts of Congress and this committee, in particular, in reauthorizing these programs in previous cycles and look forward to continuing our partnership this year.

As Dr. Marks will speak about PDUFA in his testimony, I will focus my opening remarks on the Generic Drug User Fee Program, or GDUFA, and the Biosimilar Drug User Fee Program, or BsUFA.

These programs have allowed FDA to provide access to affordable, high-quality medicines to millions of people who otherwise could not afford them. Facilitating access of lifesaving medicine for all Americans is a top priority for FDA.

Since its creation more than ten years ago, GDUFA has allowed the agency to approve thousands of generic medicines resulting in significant cost savings for consumers. By some accounts, generic drugs saved the U.S. healthcare system more than \$2 trillion over that period.

Patients' confidence that generic drugs will work the same as brand products and can be freely substituted is the foundation for the access and savings that generics have produced for the healthcare system.

We are committed to building on the success by approving more drugs in a single round of review, including complex generics with little or no competition.

With more generic drugs on the market, there is a corresponding increase in the need for FDA advice over the lifecycle of these products. Indeed, we see a steady increase in generic drug applications with post-approval actions.

In addition, as brand name drugs become increasingly sophisticated and harder to manufacture, the generic program faces increased demand to keep up with innovation.

GDUFA III will build on the agency's prior success by introducing new measures that allow for earlier approvals and ensure that we have appropriate staff expertise to deliver on our goals year after year.

Let me now turn to the Biosimilar User Fee Program. The abbreviated biosimilar approval pathway saves the developers time and resources, thus encouraging competition and potentially lowering healthcare costs.

Since the enactment of BsUFA II five years ago, the number of approved biosimilar products has grown from five to 33 today, including an interchangeable insulin product.

BsUFA III proposed to retain the majority of existing review performance goals with changes to some of the meetings between FDA and developers to improve communications.

With a growing portfolio of approved biosimilar products, the proposal seeks to expedite the review of new indications for other changes after the initial approval.

Finally, BsUFA III doubles down on efforts to advance the development of interchangeable products that may be switched at the pharmacy, like generic drugs, resulting in even greater access to lower cost biosimilars.

To close, I cannot emphasize enough the critical importance of re-authorizing these three User Fee Programs. Without them, FDA's medical product programs which have allowed for hundreds of treatments and cures for life-threatening disease could not exist as they are today.

PDUFA's revolutionary impact on innovation and the flow of new medicines is matched by PDUFA's impact on making what might otherwise be thousands of unaffordable drugs accessible to millions of Americans.

As the BsUFA Program continues to grow, we anticipate that it will complement PDUFA by expanding the availability of even more high quality, affordable medicines for all those who need them.

Thank you, again, for the opportunity to be here today. I look forward to your questions.

[The prepared statement of Dr. Cavazzoni follows:]¹

[Please see footnote.]

Ms. ESHOO. Thank you, Dr. Cavazzoni.

Now I would like to recognize Dr. Peter Marks.

Welcome back to the committee, Dr. Marks. Thank you for your really extraordinary leadership, and you have 5 minutes to make your presentation to us.

STATEMENT OF PETER MARKS, M.D., Ph.D.

Dr. MARKS. Thanks very much.

Madam Chair, Ranking Member Guthrie, and the members of the subcommittee, I am Peter Marks, Director of the Center for Biologic Evaluation and Research at the Food and Drug Administration.

We are excited to be here today to work with you to initiate the congressional reauthorization of the User Fee Program. For my portion of the testimony, I will focus on the Prescription Drug User Fee Program, or PDUFA.

Both CDER and CBER implement the commitments contained in the PDUFA commitment letter, which are referred to as PDUFA VII. So know that while I am presenting the elements of the PDUFA VII letter, both Dr. Cavazzoni and I share the responsibility to oversee the program.

Since first enacted 30 years ago, PDUFA has revolutionized the United States' drug approval process. It has reversed the lag in drug approvals that prompted its creation, providing Americans with more timely access to safe and effective medical products.

Today almost two-thirds of new active substances approved globally are launched first in the United States. It is not an understatement to say that there are many people with us today who would not be here without the program, which has dramatically reshaped drug development and approval in the United States, bringing potentially lifesaving therapies to patients in a much more timely manner.

So it began with a general focus on shortening review times through successive five-year PDUFA reauthorizations. Program enhancements have evolved and expanded significantly.

Enhanced interactions give us the opportunity to provide more guidance to sponsors, improving the potential for first cycle approval and giving safe and effective drugs to patients sooner.

These interactions also enable sponsors to incorporate the advances in regulatory science so their development programs are expediting drug development and facilitating timely regulatory decisions.

Reauthorization of PDUFA will enable the agency to collect fees to support the review of new, innovative drugs. The PDUFA VII commitment letter includes the following categories, among others: enhancing CBER support for the development, review, and approval of cell and gene therapy products and new allogeneic extract products; advancing applied scientific research to expedite drug development; continued enhancement and modernization of the drug safety system; advancing the utilization of innovative manufacturing technologies; and improving FDA's hiring and retention of key scientific and technical talent.

As the Director of CBER, I would like to direct your attention for a moment to the PDUFA VII commitment focused on new enhancements to CBER support the development, review, and approval of cell and gene therapy products and new allogeneic extract products.

FDA has experienced exponential growth in cellular and gene therapy submissions over the past seven years with close to 2,000 active development programs. We have seen a sustained increase in development program activities, including an 85 percent in-

crease in investigation of new drug applications and a 158 percent increase in formal meeting requests.

A number of these programs have the potential to bring new therapies to meet unmet medical needs to serious and life-threatening diseases. Since December 2016, 68 of 180 requests have received regenerative medicine advanced therapy, or RMAT, designation, which was enacted by Congress as part of the 21st Century Cures Act, and three of these designated products have received approval in 2021. These include two allogeneic cellular products, one for children with a rare immune disorder, one for wound healing, and a third, CAR T-cell gene therapy product for B-cell lymphoma.

To meet the demands of this rapidly expanding cell and gene therapy portfolio, PDUFA VII proposes new enhancements to CBER's capacity. The proposal will allow the agency to produce multiple guidances, both public meetings to examine new technologies and approaches, patient-focused drug development meetings to better understand patient perspectives on gene therapy products, and public outreach to facilitate product approval and development and approval.

New allogeneic extract products also will be included in PDUFA VII, and the program will provide needed resources to facilitate the development and approval of new medical products critical for the diagnosis and treatment of allergies, including serious food allergies.

Enhanced cell and gene therapy and allogeneics are just two examples of the important enhancements proposed under PDUFA VII, and we will be happy to answer your questions regarding the others.

Thank you, again, for your time today.

[The prepared statement of Dr. Marks follows:]¹

Dr. MARKS. Thank you, Dr. Marks.

A little housekeeping issue. Since our witnesses are virtual today, I am asking members to mute their mikes after they ask their question so we can hear the witnesses more clearly. When you are unmuted, it, I think, drains away some of the power and the clarity of whomever is speaking.

So thank you for that.

All right. I think that we will now move to questions of our witnesses, and I recognize myself for 5 minutes .

I leaned over and said to our ranking member that these programs have all worked. Members from both sides of the aisle support these programs, and they continue under your direction and your leadership to keep producing good things for the American people.

PDUFA was first passed 1992. Congress has successfully, reauthorized the program five times since then. For anyone that is tuned in today listening to our hearing, they have already heard a real alphabet soup of acronyms.

What I want to ask each one of you is what are the highlights of the reauthorization of these three programs. What is brand new?

Is there a commitment of more dollars for each program? Does it remain the same?

And how long does it take for you to negotiate these agreements, as well, in meeting with industry partners?

So if you could just highlight what is new, what you are excited about that has been brought forward by both the FDA and industry, and also the resources.

Dr. CAVAZZONI. Madam Chair, thank you.

I am happy to start and focus on the generic and the biosimilar programs and let Dr. Marks speak more to PDUFA.

First, to your question about resources, all three reauthorization proposals entail incremental resources for FDA, and those resources are largely overwhelmingly pointed to incremental staff to meet the additional enhancements and commitments in the proposals.

When it comes to the generic program, the agreement is really focused on increasing the efficiency of the review process and trying to make the most out of every single review process so that we can increase the proportion of generic drugs that are approved with only one cycle of review.

And to that effect, there are a number of incremental elements in the proposals to achieve those goals.

The other big focus in the generic program is enhancements to facilitate and accelerate the development of complex generics, which are those complex generic drugs that are more difficult to make.

And to that effect, the agreement includes commitments to issue product-specific guidances to increase communication with the manufacturers who are developing these complex generics and also to ensure that there is communication in situations where we have to issue a complete response letter and move the application to review.

With biosimilars, the focus of the proposal is really about increasing the efficiency of the biosimilar development, and within that is the approvals of interchangeable biosimilars, which are those biosimilars that can be switched at the pharmacy like generics.

And we have already seen some gains there with the approval of interchangeable biosimilar insulin this past year.

I am going to yield the time to Dr. Marks to speak to PDUFA.

Ms. ESHOO. OK. Dr. Marks.

Dr. MARKS. Thanks very much.

I will try to be brief, but these commitments take a lot of time to work through, and approximately two years has gone into leading up to arriving at the agreements.

In the PDUFA commitment, some really important enhancements include an early meeting type called the Interact Program for both the Center for Drugs and the Center for Biologics, which will allow manufacturers to get early input on their development programs.

It also includes and we have already heard about the STAR Program which will be a way that supplements can be split and reviewed in a somewhat more timely manner, hopefully bringing them towards approval for additional indications for already approved drugs at least a month earlier.

And we also have an incremental increase in our cell and gene therapy staff which is desperately needed to allow those products to move ahead and progress in a very timely manner.

Thanks.

Ms. ESHOO. Thank you very much.

The Chair now recognizes our ranking member, Mr. Guthrie, for his 5 minutes of questions.

Mr. GUTHRIE. Thank you, Madam Chair.

I really appreciate it, and it is great to be here to get these moving forward.

Just before the committee started, we had a discussion up here with the Chair and Dr. Burgess, and we were just talking about how do we get drugs out quicker to the marketplace which we know are safe and effective and out to the marketplace quicker.

And since we do not really have the chance to get FDA before us too often, Dr. Cavazzoni, I just want a question about Aduhelm, and my question is was FDA asked to consult with CMS.

The situation with Aduhelm is that FDA had an approval and CMS said send it back for more analysis. So I just wondered if 150 makes the approval, why the coverage determination asks for more analysis.

And so my question for you, Dr. Cavazzoni, just to put the background, was FDA asked to consult with CMS, ensure its analysis of Aduhelm when the decision was made to cover the drug only with evidence development?

Dr. CAVAZZONI. So thank you for that question.

The FDA and the CMS decisions are independent of each other. FDA makes a determination that a drug is safe and effective, and in this case we did so by approving Aduhelm, and then once that decision is made, CMS makes their own decision on coverage on the basis of their parameters and standards and process.

The data that served as the basis for the approval of Aduhelm was available to CMS and the public, in fact, because we have shared all the reviews and the memos at the time or shortly after approval. And so those data were, you know, well known.

CMS, you know, makes their own decision based on their criteria and their thinking about the data.

FDA is the agency that determines that a drug is safe and effective.

Mr. GUTHRIE. You answered my question on that. So I understand what you are saying is they are independent and should be. But if the FDA says it is safe and effective and CMS says, "No, we are going to need more data to understand that," do you think that the mandated trials that CMS is asking for are duplicative?

Dr. CAVAZZONI. I was not part of nor were we part of the thinking by CMS in making these determinations. What I can say is that based on FDA standards, we determined that the drug should be approved using accelerated approval, which is a pathway that inherently has [audio malfunction].

Mr. GUTHRIE. OK. Just one question on that, if I could ask you a question on that. I am sorry.

So because we have had other things that have been accelerated approvals, and it is important that people understand this.

So what is the difference between FDA accelerated approval standard, safety standards and additional approval process?

Dr. CAVAZZONI. Thank you.

That is a very, very important question. The accelerated approval is based on some surrogate endpoints that predict clinical benefit or some intermediate clinical measures.

And because of that, we often, if not all the time, require post-approval studies or confirmatory trials. So in the situation, in the instance of Aduhelm, we determined that the data met the criteria for using accelerated approval as opposed to traditional approval, which normally does not require the confirmational additional post-market studies except for safety in some instances.

Mr. GUTHRIE. So if I am a patient in that, what was the difference in safety?

Is the drug going to be safe if you do accelerated approval? Because we have that currently in our country right now.

Dr. CAVAZZONI. Yes. So when we make the determination that the drug can be approved under accelerated approval, we determine that the benefits outweigh the risks for the drug and that the drug can be marketed and used by prescribers with information that is provided in the prescriber information or the label.

Mr. GUTHRIE. Do not have but about 20 seconds left. So do you believe that CMS' decision to not accept accelerated approvals in that way will hurt other further research in Alzheimer's moving forward?

Dr. CAVAZZONI. There have been some concerns raised about this. Our focus is to review these drugs. There is a very, very rich pipeline for Alzheimer's, and we expect to have a lot of work ahead in advancing the development of these drugs.

Mr. GUTHRIE. Thank you.

My time has expired, and I yield back.

Ms. ESHOO. The gentleman yields back.

The Chair recognizes the chairman of the full committee, Mr. Pallone, for his 5 minutes of questions.

Mr. PALLONE. Thank you, Chairwoman Eshoo.

As I mentioned in my opening statement, it is critical that Congress reauthorize User Fee Programs on time, well ahead of the September 30th funding deadline. So my question is to help all committee members understand the importance of passing these agreements, Dr. Cavazzoni and Dr. Marks, can each of you describe briefly what would happen to your centers at FDA if we enter August or even September and Congress has not acted.

And what would that also mean for patients, if you would?

Dr. CAVAZZONI. Thank you, Chairman Pallone.

I am able to start.

I am not exaggerating by saying that not reauthorizing these programs will be disastrous for FDA and for patients.

These programs represent the funding for the bulk of, well over 80 percent of our medical product staff, and that represents well over 5,000 staff in the agency.

And these staff are, of course, critical for reviewing applications and for making sure that we continue to have this incredible flow of new drugs or new, affordable generic drugs for the American

people, which these programs have been able to bring to us over the years.

I will yield to Dr. Marks for some additional comments.

Dr. MARKS. Thanks, Dr. Cavazzoni.

I would just echo what Dr. Cavazzoni said. Basically our ability to review novel cell gene therapies and innovative products would be basically devastated. It would be an incredible blow to our gene therapy leadership.

The United States is generally considered the global leader in innovation in gene therapy, using novel technologies such as genome editing, et cetera. And our ability to provide advice to sponsors to move those programs forward would be really crippled.

Mr. PALLONE. Thank you both.

I wanted to ask Dr. Cavazzoni about one specific area of the Prescription Drug User Fee Agreement which relates to confirmatory studies for drugs approved through the accelerated approval pathway.

Unfortunately, the confirmatory study may take months or years to get off the ground if it ever gets started at all, and in PDUFA, FDA has committed to getting the process started earlier on its end by telling sponsors about its expectations for post-marketing requirements earlier, before the PDUFA action goal date.

So, Dr. Cavazzoni, explain how these pre-approval communications will help post-marketing studies start earlier.

And then what more could be done to ensure confirmatory trials begin on time and are completed?

For example, would it be helpful if manufacturers were required to begin enrollment in post-marketing studies before FDA approves their product?

Dr. CAVAZZONI. Thank you, Chairman Pallone, for that excellent question.

So you mentioned PDUFA introduces some new performance goals for FDA to review proposals for post-marketing requirements and to communicate to the manufacturers in a timely fashion when those post-marketing requirements are needed.

When it comes to confirmatory trials, those are an inherent component of the accelerated approval program, and we do agree that whenever possible the confirmatory trials should be underway by the time the approval takes place and ideally should have started recruitment.

There may be some instances where that may not be possible.

The other very important aspect of accelerated approval is our ability to quickly and efficiently withdraw the drug from market in those situations where the confirmatory trials do not confirm clinical benefit.

And right now the process that we have is very cumbersome and can take months to years because it is heavily dependent on the manufacturer's willingness to withdraw the drug when we ask them, and if they do not, then we have to engage in a very cumbersome administrative process that takes time and a lot of resources.

Ms. ESHOO. The gentleman yields back.

It is a pleasure to recognize Mrs. McMorris Rodgers, the ranking member of the full committee, for her 5 minutes of questions.

Mrs. MCMORRIS RODGERS. Thank you, Madam Chair.

We need to get our lives back. We have vaccines available with a second fully approved this week, and part of that transition is ending the public health emergency.

However, it is imperative that the tools we have to fight COVID-19 remain available for those who need and want them as we look to the end of the public health emergency.

So I had a few questions in that vein. Does FDA have the authority to continue authorizing vaccines and treatments for emergency use if the public health emergency were to end?

Dr. CAVAZZONI. Thank you, Congresswoman.

I will get us started, and then Dr. Marks can.

So when the public health declaration ends, the department, HHS, has the ability to keep the emergency use declaration in place, and by law there is also a requirement for public notice, a Federal Register notice, before stopping the emergency use declaration.

And so when the emergency use declaration ends after all of these tests and determinations that it should end, we also anticipate that there will be a need for some patients to continue to have access to these drugs even if once the emergency declaration ends they are considered not approved.

And so we recognize a period sort of, of transition to ensure that drugs remain available for patients.

Mrs. MCMORRIS RODGERS. OK. OK. Thank you.

I have a few more questions here.

So are you planning, are you making plans now to make sure that the vaccines and therapeutics, which do not yet have full FDA approval, are able to seek approval in a timely manner?

Dr. CAVAZZONI. Yes. And this is, in fact, the way we work with all manufacturers. From the very beginning—

Mrs. MCMORRIS RODGERS. OK.

Dr. CAVAZZONI [continue]. They come in for emergency use.

Mrs. MCMORRIS RODGERS. Thank you, thank you.

Dr. CAVAZZONI [continue]. For approval.

Mrs. MCMORRIS RODGERS. OK. Well, so these products will not have to start back at zero with new reviewers and teams?

Dr. CAVAZZONI. No, they will not.

Mrs. MCMORRIS RODGERS. OK. Has FDA communicated those plans to drug and vaccine manufacturers who have products authorized for emergency use?

Dr. MARKS. This is Peter Marks.

Yes, we have, and in fact, we have guidance out that actually specifically notes that as these products receive their emergency use, the sponsors should be prepared that they all will need to transition to biologics license applications for the vaccine.

Mrs. MCMORRIS RODGERS. OK. What is the status of the FDA workforce in terms of returning to normal?

I have heard some concerns that FDA is still communicating with drug sponsors exclusively through written correspondence or conference calls, not even Zoom or virtual calls.

In-person meetings offer the opportunity for a more robust dialogue between the agency and the sponsors. Do you have a plan to resume these in-person meetings?

Dr. CAVAZZONI. Right now we are still making them remote, and we have the ability to conduct meetings via teleconference or video conference, which have greatly increased our efficiency and effectiveness at a time when our staff are dealing with an unprecedented increase in volume of work during the pandemic.

So we recognize that once the situation normalized that we——

Mrs. MCMORRIS RODGERS. OK. Well——

Dr. CAVAZZONI [continue]. Resume some meetings, but will continue potentially to have some remote meetings.

Mrs. MCMORRIS RODGERS. Sooner rather than later would be great.

I heard the FDA had a good meeting with LuMind, the IDSC Foundation, Down's Syndrome Foundation, on what is needed and how to encourage more studies so that we know how the drugs and biologics work for those with Down's Syndrome.

I appreciate that, and I want to know if and how the programs in the User Fee Agreements support the development and validation of tools that take into account unique populations like those with Down's Syndrome.

Dr. MARKS. If you would like I can.

There are specific arrangements in the USER Fee Reauthorization, such as the Rare Disease Endpoint Pilot Program, that are put there to try to help facilitate the more rapid development of medical products for specific populations, and some of those tools can also be applied to more common diseases as well.

Ms. ESHOO. The gentlewoman yields back.

The Chair is now pleased to recognize the gentleman from North Carolina, Mr. Butterfield for his 5 minutes of questions.

Mr. BUTTERFIELD. Thank you, Madam Chair, for convening this very important hearing today, and thank you for your leadership.

Madam Chair, further delay should not be an option, and thank you to our witnesses for your testimony. As other members have said, thank you so much for your service to our country.

As the co-chair of the Rare Disease Caucus and the Childhood Cancer Caucus, I was pleased to see that the commitment letter addresses the importance of increasing review of combination products and advancing the development of drugs for rare diseases.

And so my first question, and I guess I will start with you, Dr. Marks; my first question regards pediatric cancer. Without question, we are accelerating cancer drug development for children. It is a good thing.

What impact has the Race for Children Act had?

And looking forward, can you explain the importance of including combination studies in the pediatric assessment?

Dr. MARKS. Yes. So thank you for that question.

So it is obviously critical that cancer drugs be studied in pediatric populations as soon as they possibly can be, and that is a critical piece of this.

Our center has worked, as has the Center for Drugs and the Oncology Center for Excellence, have all worked to try to move forward drug development programs as fast as they can to be able to move towards appropriately studying these in children to alleviate the pediatric burden of cancer.

Mr. BUTTERFIELD. Thank you for that.

And just to let my colleagues know that my fellow co-chair of the Childhood Cancer Caucus, Mike McCaul, and I have introduced H.R. 5416, the Give Kids a Chance Act. It is H.R. 5416. Please give it some attention.

This bill would authorize the FDA to direct companies developing cancer drugs to undertake pediatric study plans of combinations of new drugs, and so I look forward to working with this committee and all of you and the FDA on our shared goal of bringing hope, treatment, and cures to kids and families across the country.

Let me next go to Dr. Cavazzoni. Thank you for your testimony today, and thank you for all of the work that you do for all of us.

My next question is it pertains to the Rare Disease Input Advancement Pilot Program. As you know, most rare diseases do not have an FDA approved therapy, which is why I applaud you at the FDA for the creation of this pilot program.

Rare disease advocates have anxiously awaited for a program like this, but have raised several issues that I would like you to address.

With over 7,000 rare diseases, why is the pilot limited to one proposal per quarter?

Dr. CAVAZZONI. Thank you, Congressman.

This new pilot that was introduced in PDUFA will allow us to work with sponsors very early in development to develop or identify endpoints that can be used to study treatments for rare diseases.

This is a pilot. It is a start, and we recognize that as a pilot it will be only a certain amount of programs that we might be able to engage with sponsors on.

Having said so, we really see that is a very important start, and all of this is complementary with all the other elements in the PDUFA VII proposal that will facilitate the development of rare diseases.

For instance, —

Mr. BUTTERFIELD. Just remember we have over 7,000 rare diseases that we are dealing with, more than 7,000. So please take a look at possibly increasing that number.

Many rare diseases do not have clinical data, which has remained a significant barrier in clinical trial design and therapy development.

How will the FDA work with industry and advocates to ensure rare diseases without robust clinical data are not left out of this pilot?

Dr. CAVAZZONI. So we have a number of elements in PDUFA that includes our ongoing patient full constructed element work, including patient-focus constructive element meetings.

We also have an established program that we are continuing to advance to develop a standard set off clinical outcome assessments for therapies for rare diseases.

And so this new pilot in PDUFA VII on endpoint development really is part of a multiprong approach to continue to advance and accelerate the development of drugs for the many rare diseases.

Mr. BUTTERFIELD. Thank you to both of you.

Madam Chair, I yield back.

Ms. ESHOO. The gentleman yields back.

The Chair is pleased to recognize the gentleman from Michigan, Mr. Upton, former chairman of the full committee, for your 5 minutes of questions.

Mr. UPTON. Well, thank you, Madam Chair.

A very important hearing, and I look forward to this legislation moving forward.

I really have two questions I would like to focus on. Let me first commend our colleagues, former colleague on this committee, Richard Burr, and his partner, Senator Murray, for releasing a comprehensive pandemic preparedness package in the last couple of days. I look forward to working with them in this Congress for sure.

I would note that in the testimony presented, you stated as of December 31st, 2021, there were more than 670 drug development programs in the planning stages, and you all reviewed more than 470 trials of potential therapies for COVID-19.

It is good to hear. I commend you for work speeding up vaccines to the U.S. population, for sure, but what areas of drug development from your vantage point do you see as inadequate to meet the possible pandemics of the future?

I am worried about lack of new antibiotics. I would just note maybe you want to comment on our colleague, Mr. Doyle's PAS-TEUR Act, which was included in the H.R. 6000 Cures 2.0, which helps spur development of novel new drugs to prevent pandemics.

It has support, you know, broad support. I would urge this committee to take action on it a little bit later this year, but I am interested in your constructive ideas on how we deal with these future pandemics.

Either one of you is fine.

Dr. CAVAZZONI. Dr. Marks?

Dr. MARKS. Yes, I am happy to start with vaccines and say that obviously what we have learned is we have to have constant surveillance and constantly work to do our best to have medical countermeasures at the ready.

In some cases, this will mean working our way toward vaccines that are probably more broadly admissible for certain things; work toward obtaining a coronavirus vaccine just like there has been long-term work on a pan influenza vaccine.

So we will have to continue to work very diligently on vaccines and continuing our ability to bring forward rapid vaccine development. That was one of the advantages that have been on the mRNA platform, the ability to rapidly move a vaccine into development against a specific pathogen.

And I will turn to Dr. Cavazzoni for the drug development piece for antiviral.

Dr. CAVAZZONI. Thank you, Dr. Marks, and thank you, Congressman.

When it comes to therapeutics, the situation is really not dissimilar to vaccines. We need to continue to do surveillance for emerging new variants or viruses.

And when it comes to therapeutics, we need to continue to advance the development of antiviral drugs and specifically antiviral drugs that are less prone to lose utility or efficacy when a new variant emerges.

And we have seen some advances to that effect in the recent authorizations of oral antiviral, for instance, that have a mechanism that tends to be more sort of resilient to the emergence of new variants.

And we also have to continue to advance technology, such as platform technologies even for therapeutics in addition to vaccines that might allow us to learn from drugs or types of drugs that have been determined to be safe and effective, and apply some of what we know about those drugs to advance the development within the same platform.

Mr. UPTON. That leads right into my next question relating to real world evidence. As you may know, we have that included in Cures 2.0. It provides for advancing the use of RWE as we look down the road.

Is this going to help us ten years from now if we are able to get this thing done?

And just as a quick follow-up, would it be useful to include that as part of the pilot program, sort of building on what we heard in a question a little bit earlier?

Dr. MARKS. I can start on that one. So real world evidence is something that is clearly going to make a difference moving forward, particularly when it is used Fit-for-Purpose.

We are still early on in the days of real-world evidence because to use real world evidence, one has to have reliable data. It has to be based on reliable evidence that one is drawing from, and we are still developing computer systems from the medical record to do that reliably.

Nonetheless, it has already helped us in the vaccine world to understand the efficacy and the safety of various vaccines.

There are provisions within the current PDUFA commitment letter to continue and expand upon and build upon the world on real world evidence, and the agency has had a longstanding commitment in both centers, the Center for Biologics and the Center for Drugs, for moving ahead using real world evidence taken, for instance, from things like the Sentinel System.

Dr. Cavazzoni, do you want to add anything to that?

Mr. UPTON. I think my time has expired. I appreciate that. I look forward to following up with you. Thank you for the work that you do.

Ms. ESHOO. The gentleman yields back.

It is a pleasure to recognize the gentlewoman from California, Ms. Matsui, for your 5 minutes of questions.

Ms. MATSUI. Thank you very much, Madam Chair, for this very important hearing.

And I want to thank the witnesses for being here with us today.

Dr. Cavazzoni and Dr. Marks, thank you for CDER's and CBER's work on patients for this drug development in recent years. Highly rigorous clinical research around the safety and effectiveness of therapies in development is critical, but does not always consider the full picture of the potential impact of a new treatment.

And that is especially true for rare conditions, such as Duchenne Muscular Dystrophy. With a spectrum of presentation in patients, as well as many comorbidities, the potential effects for the therapy are not always linear, nor are the risks and benefits.

Therefore, it is equally critical to include this patient experience data when you are viewing a potential new treatment, and that is why I have introduced the BENEFIT Act. That is legislation to strengthen patient-focused drug development, or the PFDD approach.

Dr. Cavazzoni and then Dr. Marks, patients and drug developers are interested in working in this space, but the clear communication about how FDA considers PFDD in making regulatory decisions, what is FDA's plan to explain to stakeholders how data related to patient experience and perspective can be found in the drug review process?

Dr. CAVAZZONI. Thank you, Congresswoman.

I am happy to start. The PDUFA VII agreement entails a number of enhancements that build upon the Patient-Focused Drug Development Program that has been part of PDUFA in the current cycle.

So we are planning to continue to hold patient-focused drug development meetings, to continue listening sessions and engagement with patients, developers, and the communities to work to find ways to increase the inclusion of patient experience and endpoints that are meaningful to patients in clinical trials.

And one of the important vehicles that we are going to be using is to issue guidance. We have four guidances that are currently in development and will be issued in the near future that will provide developers and patient communities information and advice on the development of endpoints and core outcome assessments.

Ms. MATSUI. Thank you.

Dr. Marks, do you have any more to add to this?

Dr. MARKS. No, I think Dr. Cavazzoni covered it well.

Ms. MATSUI. OK. Thank you.

Now, I have heard concerns from providers about recent modifications of the risk evaluation and mitigation strategies, or REMS, for Clozapine, and it is an important medication used to treat patients with schizophrenia.

Now, implementation issues with the new Clozapine REMS this past November posed excessive burdens on healthcare providers and put patients at risk, leaving FDA to suspend the provisions after just four days of operation.

Stakeholders are now seeking clarity on how long the suspension will be continued and what steps FDA is taking to incorporate stakeholder participation in REMS' development.

Dr. Cavazzoni and then Dr. Marks, unless Dr. Marks should go first, how is FDA communicating its plans on REMS with stakeholders, including prescribing physicians and pharmacies?

Dr. Marks, do you want to go first?

Dr. MARKS. So in our case the REMS affected in our center was one for a medication that is used to actually treat complications that relate to the administration of chimeric antigen receptor T-cells.

And the way we communicated that was through guidance in terms of a modification to the REMS that will be in effect during the pandemic. It is a little bit of a different situation than Dr. Cavazzoni's, and I will turn it over to her.

Ms. MATSUI. Yes. Dr. Cavazzoni?

Dr. CAVAZZONI. Yes. Thank you. I really appreciate the question. We are very well aware of the challenges that have been encountered with the Clozapine REMS, and this was due to the sponsor deciding to transition the technical platform that supported it.

We engaged extensively with stakeholders, patients, professional associations, and other groups before the change and after the change, and we decided to suspend some elements because of that ongoing dialogue that allowed us to learn very quickly that there were problems.

So we will continue to communicate, and we will determine when these REMS, all the elements can be reinstated, and we will only do so when we are sure that the sponsors have fulfilled their responsibilities to get this new platform working as it should because we do not want patients with schizophrenia to go without their medication.

Ms. MATSUI. Well, absolutely, because that can cause extreme problems, as you know.

Ensuring patients have access to this medication is necessary to really prevent adverse outcomes, such as hospitalizations or loss of life, and so I encourage you to address this issue expeditiously.

So thank you, Madam Chair, and I yield back.

Ms. ESHOO. The gentlewoman yields back.

It is a pleasure to recognize Dr. Burgess of Texas for his 5 minutes of questions.

Mr. BURGESS. I thank the Chair.

And, Dr. Marks, let me thank you for the last two years of this pandemic. You have always been responsive to my questions, and I appreciate you coming and talking to our Doctors Caucus at least virtually on more than one occasion. So thank you for your leadership during this time.

Now, Chairwoman Eshoo to kick us off said she wanted to see us get back to normal. I do want the country to get back to normal, but I am not sure I want to see the FDA get back to business as usual. I do not know that the status quo prior to the pandemic would necessarily be to anyone's advantage.

So over the past two years, we have seen the FDA work with this historic capability that was granted under Operation Warp Speed. Let me just ask you, and this may be a longer question that is going to require a written answer, but are there any authorities or flexibilities granted under Operation Warp Speed that the agency could incorporate into the regular processes outside of a public health emergency?

Dr. MARKS. So I am happy to start.

Thank you very much for that question, Congressman.

Probably the most important piece that I would say is actually one that is a resource intense one, but that has been the dialogue that we have had with sponsors starting very early on and going on continuously through the drug development process.

I can tell you that the vaccine development process often had back-and-forth with the vaccine sponsors where in 24 hours there has been turnaround of multiple questions. Now, normally in development that same process might take over a month.

So that type of turnaround is not something that we need new authority for, per se, but one where it is incredibly resource intense.

And I will turn it over to Dr. Cavazzoni.

Dr. CAVAZZONI. You know, the best time [audio malfunction] the emergency use authorization will not be in place at some point. We have continuously been taking stock of what we have learned during the pandemic and the experiences, and we intend to carry forward some of those lessons learned.

So, for instance, when it comes to——

Mr. BURGESS. Let me just interrupt you there because my time is limited, and I am going to ask you to respond to that in writing because that is a critical part of this, and quite honestly, I am not sure that our language we are proposing in the user fee agreements is going to cover that, but I think it is important that it needs to.

One of the other issues is the acknowledgement of risk in the process, and I think it has been really powerful that the Federal Government has been willing to assume some of the risk in the development. There was actually, once getting through the approval process, there was actually a product on the shelf if we did have a breakthrough, if something was effective.

And, again, I just want to stress that it is important we develop the language in the user fee agreements that will allow that to happen.

But let me just ask a question on the emergency use authorization since that came up, and my concern is that you have something that may be effective, and so it is going to undergo an emergency use authorization evaluation.

But there are instances. For example, a patient in the ICU, sick with coronavirus, there are no medicines on the shelf. Remdesivir does not work that late in the course of the illness. Steroids if they are going to have worked will have already worked, and now they are past their utility.

But there are some newer products, what are called vasoactive intestinal peptides that are showing a great deal of promise.

The difficulty right now is they cannot even get to the emergency use authorization stage because they are still collecting data in the Phase 3 trials. The question is you have got an ICU population who is terribly sick; a disease that is taking 3,300 patients a day in this country right now. We are just fixing to have another candlelight vigil for all of the people that we have lost.

What can you do to make that emergency use authorization process a little more straightforward when there is obviously indication that the product is going to be useful?

Dr. CAVAZZONI. So when it comes to the emergency authorization, while the [audio malfunction] may be different from approval, we still need to have some data that show that the known and potential benefits outweigh the known and potential risks.

Mr. BURGESS. Yes. Let me just interrupt you there for a second because my time is going to expire. This is critically important.

You already got an indication because it is in a Phase 3 trial. So it is already showing some efficacy, and again, we are talking about a population of patients that has virtually no other recourse.

So this is the difficulty that I am encountering. We talk about real world stuff. In an ICU earlier this week, this very question was posed to me, and I do not have an answer for it, but I know we need one.

So I am asking you two at the agency to help us develop an answer for this.

Dr. MARKS. The answer——

Mr. BURGESS. Yes, sir.

Dr. MARKS. The answer is probably the use of our expanded access provisions, which we have actually used quite effectively, and the Expanded Access Program both in a patient and intermediate treatment size population allows us to give investigation [audio malfunction] to thousands of individuals potentially with very simple protocols, such as informed consent and capturing safety information.

Mr. BURGESS. Well, currently these patients are being treated under right to try. It does not seem ideal.

Thank you, Madam Chair, I will yield back.

Ms. ESHOO. The gentleman's time has expired.

The Chair now recognizes the gentlewoman from Florida, Ms. Castor, for your 5 minutes of questions.

Ms. CASTOR. Well, thank you very much, Chair Eshoo, and thank you to our witnesses for appearing today and to your service to the country.

The user fee reauthorization process really provides the Congress with an opportunity every five years to review FDA's authorities to determine what is working well, what can be improved, and how Congress can better provide the agency with the tools and resources for innovation and keep the American people safe.

The FDA's enforcement authorities are a critical component of this mission to ensure that American consumers can have confidence in the products regulated by the agency, that they are safe to use, and this includes FDA's ability to issue warning letters, to conduct inspections, issue fines, and begin legal proceedings when appropriate.

In the case of certain products, including food products or medical devices, controlled substances and vaccines, FDA has the authority to issue mandatory recall to remove a product from the market should the agency determine that it is necessary to protect health and safety.

However, many may be surprised to know that the agency lacks this authority for the majority of drugs that Americans take every day, including prescriptions and over-the-counter drugs. Instead FDA and the American people must rely on the manufacturers themselves to voluntarily recall drug products when the agency determines that they are no longer safe or they are adulterated or they have been mislabeled.

And this has become a high-profile topic because in the spring of 2020, Americans were desperate to keep themselves safe from COVID-19 and the demand for hand sanitizer grew, and sadly, FDA's recall list for harmful hand sanitizers or sanitizers with failing standards grew as well.

The agency was unable to issue mandatory recalls. Sometimes it would take weeks or months before these dangerous or faulty products were taken off the shelves.

Dr. CAVAZZONI, while I understand that typically manufacturers have voluntarily recalled drug products from the market and that FDA has determined should be removed, what advantages would the agency experience by having mandatory recall authority for dangerous drugs?

Dr. CAVAZZONI. Thank you, Congresswoman.

I have to say that our inability to mandate recalls for most drugs is a real gap for us, and the example that you provided when it comes to hand sanitizers is a very good one.

In that instance, we became aware through our surveillance that hand sanitizers were contaminated by methanol, which is a poison that the use of that hand sanitizer led to deaths, blindness, and other very severe injuries.

And rather than being able to quickly mandate the recalls, we had to work with each single manufacturer to do so, and some of them were very responsive, but some of them were not, and to the point where we had to publish a list of contaminated hand sanitizers while we were continuing to try to persuade the manufacturers to recall the contaminated product.

And so we think that, you know, just an ability to mandate recalls is an outlier even across FDA products, and it is also an outlier when we look at the authorities of other major regulatory agencies throughout the world.

Ms. CASTOR. So what harm could come if we do not grant FDA this authority?

Dr. CAVAZZONI. Well, using the example that I just used, there may be egregious instances where manufacturers downright decide not to recall a dangerous product or there may be instances such as what we have seen with the hand sanitizers where it may take weeks for us to work, persuade the manufacturer, and during that time the publics are exposed to harmful, if not lethal, contaminants in drugs and products.

Ms. CASTOR. Thank you very much.

Madam Chair, I yield back my time.

Ms. ESHOO. The gentlewoman yields back. She has raised an excellent point, and the authority for the FDA to have mandatory recall power is contained in the Competes Act that was debated and will be up for a vote in the House this week.

The Chair is now pleased to recognize the gentleman from Virginia, Mr. Griffith, for your 5 minutes of questions.

Mr. GRIFFITH. Madam Chair, in honor of my friend Wiley Nelson, I yield one minute to Dr. Burgess.

Mr. BURGESS. I thank the gentleman for yielding.

Dr. Marks, if we could just go back to the previous conversation we were having, we have all had acquaintances, friends, staff members, families where they end up in the ICU, and there is literally nothing, literally nothing else to offer.

Again, help us with the ability to evaluate a product that seems to show some promise. It is not that there is zero promise. It is in a Phase 3 trial, for crying out loud. So it obviously got there because of showing some efficacy.

And what we lack at this point is a guard for Right to Try legislation that was signed into law a couple of years ago that does deal with some of the liability issues. It does not help with the cost. The company that is making the product available is doing so at cost, and that is not a viable business model as a long-term proposition.

So help us. Help us help people that are stuck in this situation.

Dr. MARKS. So, Congressman, understood, and I think the best I can say right now is that I think we have been very committed to trying to use whatever provisions we have at our disposal to ensure access, be that our standard access provisions or have conversations about when products were ready to come in for emergency use authorization.

I think we will look forward to trying to ensure that there is access to meet needs as quickly as we can.

Mr. GRIFFITH. I thank you. I thank you for your answer, but we need to move quicker when you have your college roommate pass away and there might have been something to help him. It makes you feel like you have got to do something when you sit on this panel.

All right. That is it. I am aware of at least a couple of recent REMS, risk evaluation and mitigation strategy rollouts that have gone poorly, wreaking havoc on the industry, and in some cases creating a real risk of patient harm.

Dr. Cavazzoni, how does the FDA keep track of lessons learned from situations like this?

Because you already said you have got input previously from the doctors when answering Congresswoman Matsui's question.

But the physicians I have been talking to and others working in the industry believe that you did not get enough stakeholder input ahead of time.

So how do you learn those lessons?

Dr. CAVAZZONI. Well, thank you, Congressman.

The problems that we have with REMS were through the company that owns the platform that delivered these REMS deciding to get out of the REMS business, and so the manufacturers have to find other vendors and other platforms that could support these REMS, such as the Clozapine REMS, the iPLEDGE REMS, and so on.

So we knew that this transition was going to happen, and to that effect we engaged prescribers, pharmacies, and other stakeholders months before this transition to get—

Mr. GRIFFITH. Well, I appreciate that and hope that the lessons from this will be learned and we will get more input sooner.

I have got to move on to other questions. Dr. Marks, last month the British publication Lancet published a study that found antimicrobial resistance. AMR is a leading cause of death around the world, more than HIV or malaria. The study used 2019, meaning the problem could be much larger if, as many believe, COVID is making resistance worse.

How worrisome is the rising trend of the antimicrobial resistance? How big a deal is that to you all at the FDA?

And as a subpart of that while you are answering that, are you looking at Phage Therapies, something I think we ought to be taking a good look at?

Dr. MARKS. So thanks very much for that question.

So obviously the Center for Drugs handles antibiotics, but we handle Phage Therapy. It is, to stay short, it is a tremendously important problem because if we run out of effective antibiotics, we will have tremendous problems, especially in our hospital and ICU environment.

We have been aggressively working with sponsors developing Phage therapies. This is a very interesting area because these are products that are highly targeted. They may have to be individualized for particular patients. So we are working through the needed regulatory paradigms, and we will look forward to continuing working this area.

Mr. GRIFFITH. So let us know how we can help.

That being said, do you believe we have enough drugs in the pipeline to meet increasing challenges of the antimicrobial resistance?

Dr. MARKS. I am going to defer to Dr. Cavazzoni for the complete response, but I would probably say the answer—

Mr. GRIFFITH. Well, answer yes or no. Do we have enough or not?

Dr. MARKS. No.

Mr. GRIFFITH. Because I do not have much time left.

Dr. MARKS. No.

Mr. GRIFFITH. OK. I got a “no.” I appreciate that.

I will tell you another thing that is interesting about the study was because we have always believed that the antimicrobial resistance was going to be showing up in areas where we used it a lot. This study says it is worst in Sub-Saharan Africa and Southern Asia where they do not use the antibiotics as much.

Very curious. Do not have an answer; do not expect one. It is just something to think about.

I yield back. Thank you, Madam Chair.

Ms. ESHOO. Right to the point, Mr. Griffith. Thank you.

The Chair is happy to recognize the gentleman from Maryland, Mr. Sarbanes, for 5 minutes of his questions.

Mr. SARBANES. Madam Chair, thanks very much for holding this hearing.

I want to thank our witnesses for their testimony today.

Obviously, as we all know because we have been focused on it for years now, the price of prescription drugs has been increasing. It is an overwhelming burden for so many Americans out there, including obviously my constituents in Maryland as well as families across the country.

And one of the agreements that we are talking about today is the Generic Drug User Fee Amendments, which play a large role in how generic drugs are reviewed and approved by the FDA.

Once approved, as we know, these generic drugs are often considerably less expensive than brand name drugs. However, in fiscal year 2021, the FDA approved only 17 percent of abbreviated new drug applications, or ANDAs, for generic drugs during the first review cycle.

This means that companies had to resubmit these drugs for approval a second time, which of course slows the process down and means that new generic drugs can take quite a long time to be approved and to get to the individuals who need them.

Dr. Cavazzoni, can you describe how successful the implementation of GDUFA II review goals has been over the last five years and what progress has been made towards reducing the ANDA review times during this period?

Dr. CAVAZZONI. Thank you, Congressman.

So what we have seen over the past four and a half years under GDUFA II is consistent gains in making each review cycle efficient and trying to increase the amount or the number of generics that are approved after one review cycle.

We have made some gains, and the program has met its review performance metrics consistently over the years.

Now, when we look at GDUFA III, it actually introduces even more tools for us to be able to maximize the first review cycle. It introduces ways to extend the goal date depending on the type of issues that is remaining rather than moving the application to the next review cycle, which obviously can be more cumbersome for manufacturers because they have to restart the submission and so on.

And so we think that the provisions in GDUFA III will really allow us to continue to build on the progress that we have made so far to increase the proportion of first cycle approval for generics, including the complex generics, more difficult to manufacture.

Mr. SARBANES. I have got two minutes of time left with you. Could you give me an example of maybe a specific drug or a category of drugs of how the GDUFA III toolkit is being expanded to allow for that first review process to achieve kind of more success?

Dr. CAVAZZONI. I could give you the example of complex generics. These are generics that are drugs that include, for instance, the drug-device combination or are a more complex formulation or route of administration, for instance, eyedrops or inhaler, inhaled drugs, and so on.

And the GDUFA III agreement has a number of provisions that we think will really facilitate the speedier development of these complex generics, including, for instance, new goals for FDA to issue specific guidances for each product that are a "how to" compilation of how the drug should be developed and how the manufacturer could demonstrate that the drug is equivalent or bioequivalent to the branded drug.

For those complex generics, the agreement introduced some new opportunities to meet with the manufacturer. For instance, after we issue a complete response letter, there is a new meeting with manufacturers that is introduced in GDUFA III that would allow us to really explain our thinking and really focus on the problems and constructively work with the manufacturer to make the next cycle be the last cycle and really get us to where we need to go with the application.

Mr. SARBANES. Well, I am out of time, but I will just observe that that kind of technical advice and guidance obviously demands resources and capacity on the part of the agency, and that is one reason we need these important user fees in place.

With that, Madam Chair, I will yield back my time. Thank you.

Ms. ESHOO. Thank you. The gentleman yields back.

The Chair is pleased to recognize the gentleman from Florida, Mr. Bilirakis, for his 5 minutes of questions.

Mr. BILIRAKIS. Thank you, Madam Chair. I appreciate it.

First of all I want to wish a good friend or former colleague here on the Energy and Commerce Committee and now a United States Senator, Ben Ray Lujan, a speedy and full recovery.

So, Madam Chair, as the co-chair of the bipartisan Rare Disease Caucus, I believe FDA can do better to facilitate the development of rare disease therapies through better coordination and fewer bureaucratic hurdles. That is why I was interested to read in the FDA's joint testimony about ideas to build on the rare disease programs in the PDUFA proposal.

Dr. Cavazzoni, do you agree that we can be doing more to ensure coordinated efforts within the agency to advance rare disease drug development?

And can you elaborate on what additional actions FDA is committed to taking for this community that faces unique challenges in getting treatments to the patients, the treatments that the patients deserve?

Dr. CAVAZZONI. Thank you for that important question.

And we are very committed to do everything that we can to find more [audio malfunction] since there are thousands of rare diseases with a lot of permanent need.

Right now if we look at the new molecular entities that we have been approving, rare diseases represented half of our new molecular entities. So we have made significant gains, and we are continuing in that to make gains thanks to the elements that are in the PDUFA VII proposals to build upon what we have in the current cycle.

Some of the elements are that new, a rare disease pilot that allows us to sit down with manufacturers and identify anything that could be used to design clinical trials for rare diseases. [Audio malfunction.]

We also are going to continue the patient-focused drug development program, which has been very successful with over 50 patient-focused drug development meetings. We will issue guidance on clinical outcome assessments and take this multiprong exhaustive approach to continue to accelerate the delivery of therapies for rare diseases.

Mr. BILIRAKIS. I do not know. The light keeps coming off, but anyway you can hear me.

As you know, around 95 percent—Doctor, I know you know this—95 percent of the 7,000 known rare diseases have no FDA approval therapy, but affect millions of Americans nationwide.

That is why I introduced H.R. 1730, the Speedy Therapy Access Today Act, or the STAT Act, with my fellow co-chair of the Rare Disease Caucus, Representative Butterfield. This bipartisan legislation seeks to replicate the Center of Excellence model embraced by the FDA in the oncology space and thus complement and build upon the existing cross-agency work focused on rare disease and providing a stronger inter-FDA organization for rare diseases.

I am hopeful, Doctor, we can get this included, Madam Chair, in the PDUFA process.

So the next question is, again, for Dr. Cavazzoni. Considering the small patient populations and difficulties surrounding clinical trial programs for rare diseases, another program in the toolkit that can

be particularly useful to the rare disease community is accelerated approval.

Can you explain how this process has helped get drugs to treat rare diseases to market faster when there is no alternative treatment available?

Dr. CAVAZZONI. Thank you for the question.

So accelerated approval has the larger [audio malfunction] in anti-infectives and some rare diseases. In order for us to be able to use accelerated approval, we need to have a surrogate marker that reasonably predicts the clinical benefit of the drug so that particularly for diseases that are chronic and take a long time to progress, we can approve the drug earlier or we can also use an intermediate clinical endpoint.

The problem with many rare diseases, in fact, the majority of rare diseases is that we have yet to identify the biological underpinning of the disease and as a result of that, we have not identified those surrogate markers that would allow us to use accelerated approval.

We are making gains and we want to continue obviously to use accelerated approval and all our expedited pathways, but we need the science and the biology to also move as it has in oncology and cancer.

Mr. BILIRAKIS. Thank you, thank you, Doctor. I appreciate it.

I yield back, Madam Chair

Ms. ESHOO. The gentleman yields back.

Members, let's all try to stay within our time. We have a classified briefing at 1:30 this afternoon, and so I hope that we can conclude our hearing today so that we do not keep the second panel waiting and we can go off to our classified briefing and not have to return.

So with that in mind, the Chair is pleased to recognize the gentleman from Vermont, Mr. Welch, for his 5 minutes of questions.

Mr. WELCH. Thank you very much, Madam Chair.

We are in this pandemic, and it is unique, and it creates real strains on doing the inspection process. The remote inspection tool is obviously very, very important, very difficult, but really essential, and it is focused on mission critical inspections, and that makes sense.

But it does leave out generics and biosimilars, and the question I have is for Dr. Cavazzoni. How do we pick up inspections on the biosimilars and generics so that they can get to the market?

Because we do have this problem that Mr. Sarbanes just mentioned, the brutal and unrelenting price increases, and if we do not have inspections of generics, we do not have inspections of biosimilars, there is no route for them to the market. There is no competition, and the pricing pressure continues.

Dr. Cavazzoni.

Dr. CAVAZZONI. Thank you, Congressman.

And as you indicated, during the pandemic we were quite successful in using these alternative methods to physical inspection of manufacturing plants, which include a host of tools, such as exchanging documents, relying on the inspections of other health authorities, and also doing these remote assessments through cameras and technological platforms.

These alternative methods can be used in a number of circumstances.

Mr. WELCH. No, but how do we pick it up? I mean, I know they can be. What I want to know is how do we pick it up so we can get the biosimilars and the generics to be inspected.

Dr. CAVAZZONI. Yes. So we have utilized these approaches for all the instances among mission critical inspections, which include the preapproval inspections when the facility lent itself to that approach.

There are some instances because of the compliance history of the facility or because the facility has had very serious inspection findings where we have no choice but to require a physical inspection of the facility and where these alternative approaches are really not possible.

And the pandemic—

Mr. WELCH. Let me—

Dr. CAVAZZONI. Yes.

Mr. WELCH. OK. Thank you. Thank you very much.

I just want to ask Dr. Marks about the BsUFA commitment letter indicates that FDA will communicate its thinking on the use of remote inspection tools before September 2023, which really is a long way off, as the prices continue to increase.

Can you tell us anything about how these tools can be used in the field?

Dr. MARKS. So you know, we are still learning how effective these tools can be by using them, and at least at our center, we have had some mixed results with using remote inspection technology.

So we are still sorting through this because at the end of the day we have to ensure that the products that come out, once we say they are safe, are truly safe and manufactured with the quality that Americans have come to expect.

Mr. WELCH. So is there a reason why those tools should be limited to the use of biosimilars?

Dr. MARKS. No, not necessarily.

Dr. CAVAZZONI. I am happy to take that question.

There is no reason. The applicability of those tools depends on the state of the facility, and there are some facilities including biosimilar facilities, but not only those, where because of past history we feel that we have—we determine that we have to do a physical inspection and, therefore, we are not able to use these alternative methods.

So this is not an issue that applies only to biosimilars but really all of the drugs under review. We really need to make that decision.

And the stronger the quality history for that facility, the more likely we are to be able to use these alternative methods.

Mr. WELCH. OK. Thank you very much.

Madam Chair, I yield back.

Ms. ESHOO. The gentleman yields back.

The Chair is pleased to recognize the gentleman from Missouri, Mr. Long, for your 5 minutes of questions.

Mr. LONG. Thank you, Madam Chair.

And being an auctioneer, I do not think you have to worry about me going over my 5 minutes . I can talk pretty fast.

Dr. Marks, as you note in your testimony, almost two-thirds of the new active substances approved in the world market are launched first here in the United States. I hope we can advance policies that encourage innovation here in the United States, that we do not stifle innovation and make the United States less attractive for development of new treatments and cures.

One area where we need more innovation and new treatments is in rare disease space which poses unique challenges for both the industry and the FDA.

Could you speak to the challenges you see from a regulatory perspective at the FDA, as well as research and development challenges for the industry for the development and approval of rare disease medicines?

Dr. MARKS. Thanks very much for that question, Congressman.

I think that we have already touched on some of them, but the issue here is that for many of the rare diseases we do not yet have good endpoints in order to facilitate the development.

So there is a lot of work going on at the agency to try to develop the biomarkers or intermediate endpoints that can help us understand that a product is effective earlier on so that we can facilitate the development of these.

The other piece at least for us in the cell and gene therapy manufacturing area is a place where work needs to be done, and we are working with colleagues at the National Institutes of Health and through the foundation of the National Institutes of Health in a public-private partnership to try to help facilitate gene therapy manufacturing, to help that process speed along so that therapies could get to patients more quickly that way.

So combination of needing better endpoints and increasing throughput for the manufacturing process at least on the gene and cell therapy end.

Mr. LONG. And I might have missed it in your answer there, but what makes the endpoint development process particularly challenging for development of rare disease treatments?

Dr. MARKS. It is because you have a small number of patients, and it is often hard to find any particular marker that will definitively correlate with the disease outcome. Particularly in some of the rare diseases where it might take years for a [audio malfunction] to occur. So we need to be able to correlate a marker with that outcome, and that is why we very much are supporting patient advocacy groups that are doing natural history studies even ahead of drug development so that they collect the information to help determine those markers in advance of the drug development programs.

Mr. LONG. Thank you.

And I apologize if I went over some plowed ground here, but I have been here for about 90 percent of the hearing and have to step out occasionally. So if some of those questions were asked earlier, I apologize.

And I yield back a world record two minutes and four seconds.

Ms. ESHOO. Absolutely world record. Thank you.

The gentleman yields back.

Mr. Schrader was here earlier, but I do not see him, and he evidently is not on Webex. So we will move to and the Chair recognizes the gentleman from California, Mr. Cárdenas, for your 5 minutes of questions.

Are you there? No?

All right. Well, then we will go over to the Republican side. The Chair recognizes the gentleman from Indiana, Dr. Bucshon.

Mr. BUCSHON. Thank you, Madam Chairwoman, for that quick recognition. I appreciate this hearing.

First, I want to talk about why Congress absolutely needs to reauthorize these user fee agreements. They are key to helping patients in this country and increasing access to care, to allow for the continued innovation and the development of new drugs and treatments, and also this presents us with a great opportunity to learn from the successes of Operation Warp Speed on how we can reduce burdensome and unnecessary red tape to speed up drug development, as we witnessed in the development of the vaccines for COVID-19.

FDA's PDUFA VII commitments include a chemistry manufacturing and controls. CMC development and readiness pilot, a program aimed at expediting CMC readiness so the patients will have earlier access to important new products.

FDA committed to outlining the eligibility criteria for this pilot by the end of this year. I want to ask you specifically about cell and gene therapies, as those are an important and growing area for patients and, in my opinion, a key component of the future of personalized medicine.

And as you both know, they have some unique CMC issues.

Dr. Cavazzoni, can the FDA ensure that the eligibility criteria for CMC development and readiness pilot are broad enough to encompass a wide range of important products for patients, including cell and gene therapies?

Dr. CAVAZZONI. I can speak to this. I can start us off and Dr. Marks since cell and gene therapies are in his center.

We are very excited about this new pilot because this new pilot would allow earlier and more frequent interactions with the manufacturers and the centers during development when it comes to the manufacturing aspect of the drugs.

And this will have an impact, among other things, in the development of rare diseases where there is so much unmet need. And so we really look forward to this pilot and to the results that we anticipate it might yield.

I will turn over to Dr. Marks for additional comments.

Dr. MARKS. I do not want to waste your time. We totally agree that we very much think that the chemistry manufacturing control team is incredibly important in the cell and gene therapy space and totally support moving ahead and advancing this area.

Mr. LONG. Thank you.

I just urge you to get this program started as soon as possible once you have approval, and to make sure that some of the focus for the pilot is on cell and gene therapy. CMC readiness will help get these important therapies to patients earlier.

I also now want to talk about the diversity in clinical trials. As we have seen through the clinical trials for the COVID vaccines, we need to do better promoting diversity in clinical trials.

It is difficult to get a diverse population enrolled in some of these trials. I understand that, but we need to do better at promoting that, and this is something I have been advocating for.

As a doctor, I know the importance of the needed diversity participation in trials to better understand how the drug treatment and/or vaccine would respond to the different patients in our country, the different population of people in our country, just as I know from my medical training that certain diseases could and would affect certain patients differently based on factors such as genetics and ethnicity.

As the future of medicine continues to move towards personalized medicine, this will only continue to become more important, and my hope is that the FDA and industry continue to collaborate to find better ways to encourage and promote participation in clinical trials.

This is why I introduced legislation with my good friend, Dr. Ruiz, that will help promote clinical trials having proportionate representation of all communities, as well as support education outreach and recruitment for future clinical trials.

Dr. Cavazzoni, the commitment letter includes a section on enhancing the use of digital health technology to support drug development and review. The letter suggests the use of DHTs can support and enable the conduct of decentralized clinical trials.

Does the FDA believe these enhancements will be impactful in improving clinical trial diversity?

And does FDA have plans for expanded outreach around the importance and value of clinical trial participation?

Dr. CAVAZZONI. Thank you, Congressman.

We could not agree more about the importance of increasing diversity in clinical trials. And as you have mentioned, we have made some real gains in the development of vaccines and therapeutics, and we should try to maintain those gains.

One of the important tools in facilitating diverse recruitment is decentralized clinical trials, and decentralized clinical trials with the use of technologies, such as digital health technologies, to collect endpoints, our information during the trial, or also technologies to check the one that we are using today to make clinical assessments or to obtain consent from the patient.

[Audio malfunction] having to travel to a clinical investigation site.

We have really seen an example of these tools, and we look forward to——

Mr. LONG. Thank you. My time has expired.

I just want to say, if you will indulge me, Madam Chairwoman, for just a second, in the COVID vaccine space, we have seen some resistance to vaccination in certain subgroups of our population based on the clinical trials not having people of a diverse nature in those trials.

So this is really, really important.

Thank you.

Ms. ESHOO. The gentleman yields back, and I would just say to him thank you for raising the issue of diversity in clinical trials. I have legislation on it, as do you. I believe that the bills are complementary to one another and we will continue working on it.

But thank you for that. It is so important.

The Chair now recognizes the gentleman from Oregon, Mr. Schrader.

He is not here? All right. Then we will go to the gentleman from California, Mr. Cárdenas, for your 5 minutes of questions.

Mr. CÁRDENAS. Thank you very much, Madam Chairwoman and also Ranking Member, for having this very incredible, important bipartisan meeting where we are in agreement and we are working together, and we have been working together for a long time to bring this about.

Unfortunately, it is not going to be on Fox News, CNN, MSNBC, or anywhere else. It is probably going to spread out to the nerds who watch us on television, in our hearing or what have you, but I do want to say thank you so much to my colleague, Dr. Bucshon. I agree with everything you just said over the last 5 minutes -plus, and I just want to say thank you. It is wonderful to see that we agree on many things. Unfortunately, the public only thinks that we always disagree.

So I just wanted to point that out that this is an amazing opportunity for us to demonstrate that we are, in fact, getting things done on behalf of the American people.

And when it comes to the FDA, when it happened in the United States, it benefits the rest of the world and is something we should be proud of.

The user fee process ensures that the FDA has the funds it needs to evaluate and approve medical innovations and therapies in a timely manner. I want to talk a bit about patient-focused drug development, which is a systematic process that would help to center patient input in the drug evaluation and decision-making process.

Dr. Cavazzoni, again, thank you so much for your work and your dedication and your public service.

Can you talk a bit about why this focus on patient-focused drug development is a growing priority for the FDA?

Dr. CAVAZZONI. Thank you, Congressman.

This is one of the top priorities for us. We recognize that for therapies to be meaningful to patients, they have to be studied using measures that take into consideration what matters to patients in the patient experience.

And so we are really looking forward to continue to build on the major gains that we have made during the current cycle of PDUFA, to continue the Patient-Focused Drug Development Program, continue the work that we have been doing to issue grants for the development of clinical outcome assessments, and issuing guidance.

Mr. CÁRDENAS. Thank you.

Can you give a quick example of having the patient perspective incorporated into the process and how it has helped patients to this date?

Dr. CAVAZZONI. Well, for instance, an example of the patient experience is having information on how the patient experiences improvement in function when they take a drug, and that functional

improvement is very important and may not necessarily be seen even if some of the traditional endpoints show that the drug has an effect on those endpoints.

Mr. CÁRDENAS. Thank you. Thank you so much.

Dr. Marks, also thank you for your dedication and your expertise that has helped so much advancing what we do here at FDA.

The Center for Biologics Evaluation and Research will be using some of the funds to conduct patient-focused drug development activities in the evaluation of gene therapy products and regenerative medicine therapies as well. How will you ensure that the patient's experience is an integral part of the approval process for these therapies?

Dr. MARKS. Thanks very much for that question.

So much the same way as Dr. Cavazzoni has outlined, we hold patient-focused drug development meetings. We meet with patient advocacy groups and, indeed, have conversations with patients which sometimes are very revealing, particularly for rare diseases where sometimes doctors and patients have different ideas about what is the most important endpoint in their disease.

For instance, there is a certain genetic disease where there is sudden cardiac death, but it turns out that the patients did not really care about that risk. It turned out that they really cared about the fact that they were tired and terribly fatigued all the time, and they wanted that to be the endpoint sought.

So we are committed to listening to patients in this regard and then working with sponsors to try to come up with endpoints that incorporate the different nature of the endpoints into their clinical development programs.

Mr. CÁRDENAS. What are some of the nuances you will need to apply in implementing patient-focused drug development for these therapies as opposed to other types of drug therapies?

Dr. MARKS. You know, I think for cell and gene therapies they will be listening carefully to what the most important outcomes are in terms of how patients feel, function, or survive, and then potentially correlating those to intermediate endpoints or biomarkers so that we can help advance the development as quickly as possible.

So there is that linkage between what the ultimate outcome is that patients want and some intermediate endpoint to the drug development process, and that is hopefully going to help us bootstrap our way through more—

Ms. ESHOO. The gentleman's time has expired.

Mr. CÁRDENAS. Thank you, Madam Chairwoman.

Yes, my time has expired. I apologize. I yield back.

Ms. ESHOO. The gentleman yields back.

It is my understanding that Mr. Crenshaw is next, followed by the gentleman from Oregon, Mr. Schrader, and then when we go back to the Republican side, we will go to Dr. Dunn.

So the gentleman from Texas.

Mr. CRENSHAW. Thank you, Madam Chairwoman.

Thank you to the witnesses for being here. Thank you, Dr. Marks, and it is good to have you back, Dr. Cavazzoni.

It is my first time being part of the User Fee Authorization Program, and it is exciting to see where we are at and where we are going to be for the next few years.

One of the most exciting things about the PDUFA commitment letter is an expansive section of cell and gene therapies. These therapies are incredibly promising, but they lack the regulatory certainty needed to take advantage of their full potential.

One of these therapies, autologous stem cell therapies, has been met with a significant amount of regulatory uncertainty. This has led to a backwards result of innovators being unsure of how to move forward and bad actors taking advantage of loopholes, namely, the same-day surgery loophole, in the system.

For Dr. Marks, I know you have spoken at length about this problem. What can Congress do to support the FDA so that we can support innovators without flooding the market with bad actors?

Dr. MARKS. So thanks very much for that question.

Actually Congress did a wonderful thing for FDA with the passage of the 21st Century Cures Act and the medicine advanced therapies which allow us to designate therapies of promise in this space and help them to move forward as quickly as possible.

Our goal is to try to get these therapies, which I agree are potentially transformative, to patients as quickly as possible.

Mr. CRENSHAW. Do you think it is possible to regulate the safety of autologous stem cell therapies under the current designation or will these products have to seek a BLA, biologics designation?

Dr. MARKS. So we regulate these on a risk-based approach, and that is they can be regulated according to the risk that they may place, depending on how much they are manufactured and in which manner they are used.

And that risk-based approach is how we have done this, and I think it does serve patients very well in that products that have significant manufacturing are regulated under the biologics license pathway.

Whereas products that undergo minimal manufacturing and are used in the same way in the recipient as in the donor do not have to undergo that same pathway.

Mr. CRENSHAW. Thank you. I am glad to hear that. I agree with that statement, of course.

One of the challenges though in regulating these products has been with the minimally manipulated definition and broadening this definition to include adipose-derived, say MSCs—I am not going to try to pronounce Mesenchymal—which are easier to extract than stem cells from blood or bone marrow, easier to process and have high levels of effectiveness.

Now, including these in the definition might increase the number of bad actors in the market. How can Congress rewrite the definition of minimally manipulated to include adipose-derived MSCs while limiting the risk of bad actors taking advantage of that designation?

Dr. MARKS. So thanks for that.

Right now they are [audio malfunction] by a regulation, and the issue of minimal manipulation for these cells is one that minimally manipulated means generally washed or sized or things like this.

But once one uses enzymes, as one often does, when one isolates adipose-derived stem cells, or Mesenchymal stem cells, or once one puts these things into an incubator and has them grow so that you have more cells, the risk profile does change.

And we know that adverse events can occur with these. We have seen adverse events, such as when adipose-derived stem cells were injected into the eye in Florida, for instance, at CORNEX, there were several cases of blindness because there were probably residual enzymes in the injection.

So we do have to take a careful approach to these, and that is the reason for being somewhat conservative in our definition of minimally manipulated.

That said, the agency continues to always look at making sure that we are regulating these at an appropriate level to maximally bring forward effective therapies in a timely manner, while protecting the public.

Mr. CRENSHAW. It just seems that we are stuck in this process at the moment, that there is a knowledge gap that I think some of the innovators are not sure how to close.

Are there resources that OTAT would need to close this knowledge gap and understand the safety of this particular process?

Dr. MARKS. I appreciate that.

They continue to work on regulatory science in this area, and I think we will continue to work that in this area in collaboration with academic investigators to see what can advance the field.

Dr. MARKS. I am out of time. I yield back.

Thank you, Madam Chair.

Ms. ESHOO. The gentleman yields back.

It is a pleasure to recognize the gentleman from Oregon, Mr. Schrader, for your 5 minutes.

Mr. SCHRADER. Thank you very much, Madam Chairwoman. I really appreciate it.

Thank you all for being here.

Reducing drug costs remains one of my top priorities. I am proud of the work I did in Build Back Better Plan to address these costs. One of the policies that I am the lead on, along with some of my Republican colleagues, is trying to increase competition in the use of biosimilars.

You know, if we have competition, price decreases. We are having trouble, however, getting generic biosimilars into the marketplace in a competitive manner being taken up. They are routinely used in Europe, not so much here in this country.

What additional improvements do you guys think we need to make in the application process to get these products to market?

Dr. CAVAZZONI. Thank you, Congressman.

First, I would like to point out that we have made quite a lot of inroads when it comes to the number of biosimilars that have been approved. We have gone from five at the beginning of the BsUFA II cycle to now 33, including an interchangeable insulin.

And so we really are looking forward to continuing to build on this trend and bring more biosimilars to market.

Some of the elements that are important are to make the review as effective and efficient as possible, and the BsUFA proposal includes some enhancements around that.

Also, facilitating the new indications for biosimilars, and the agreement also includes some new elements there.

It is also very important that we really try to spur the development of interchangeable biosimilars so that those are the

biosimilars that can be interchanged at the pharmacy, and the BsUFA proposal has some very important enhancements, including introducing a pilot research program that would allow us to really evaluate how we can make the development of biosimilars and even more so, as importantly, interchangeable biosimilars.

That also includes issuing guidance around——

Mr. SCHRADER. Can I interrupt just for a second? I apologize, but limited time.

But on your comment on interchangeability, I guess I am pleased to hear that. I think that is a huge improvement, but I think my understanding is that at this point in time, like for instance, a change in volume of the overall product, is considered interchangeable but not the active ingredient.

What is the scientific basis for that?

Dr. CAVAZZONI. Well, this is where we need to continue to do research. [Audio malfunction] help us clarify those aspects and introduce more clarity and hopefully also more flexibility when it comes to the development of biosimilars.

Mr. SCHRADER. And I agree. Again, I just urge you to look at the active ingredients. It seems to be much more important than the volume of these products.

Now, the Federal Food, Drugs, and Cosmetics Act started in 1938. To get good endpoints, if you will, animal models were considered the best opportunity out there and probably the only opportunity to get a real idea of how a particular medication or pharmaceutical agent would respond in a living body, a mammal, rather than testing on humans.

But, you know, in the intervening years, there have been some amazing advances made and preclinical drug screening and different organs or cell cultures that can mimic human organ systems and what have you.

Is the FDA allowing use of these new technologies rather than requiring animal models in all cases?

Dr. CAVAZZONI. We recognize the need to decrease our reliance on animal models, but having said so, animal models are extremely important in drug development, particularly in determining whether the drug is safe to be put into humans for the first time.

We are working with developers, and we also have research programs internally to evaluate and qualify these alternative approaches to use of animals, and we are beginning to see some gains there, and we hope to be able to continue down that path, understanding that it may not be possible to completely eliminate our reliance on animals when it comes to drug development at least.

Mr. SCHRADER. I appreciate that. I would hope that you continue to use these alternate routes.

I would enjoy some written information since my time has run out regarding how COVID in the last four years has affected your FTE in the agency and your ability to deliver on the GDUFA, BsUFA, and PDUFA endpoints and goals from the last reauthorization.

And I yield back. Thank you very much, Madam Chair.

Ms. ESHOO. The gentleman yields back.

I especially appreciate your questions relate to biosimilars. I was the House author of the legislation to create that, but there are

many questions to be answered, I think, about the vitality of competition of products in our country.

The Chair is very pleased to recognize Dr. Dunn, the gentleman from Florida.

Mr. DUNN. Thank you very much, Madam Chair and Ranking Member Guthrie, for hosting the hearing today about the reauthorization of the FDA user fee agreements.

You know, it is my hope that the agreements that we pass this year will push the FDA to be more efficient and reliable and transparent in its review process. American biotech is leading the world in innovation, and the government agencies should rise to that moment.

I have a few process questions for the FDA panel regarding appeals in the course of events that take place, you know, following the issuance of a CRL. So please be brief in your answers, all the same reasons.

Dr. Marks, it is my understanding that the formal dispute resolution pathway provides a structured process for sponsors to resolve a scientific or a medical dispute.

That should be a simple yes/no.

Dr. MARKS. Yes.

Mr. DUNN. Yes. OK. Good. Per the agreements, the FDA then responds to that request within 30 days; is that correct?

Dr. MARKS. Yes.

Mr. DUNN. OK. Great. How often does the FDA meet that 30-day turnaround?

Dr. MARKS. I can get back to you on that for the FDA overall. For our center at least in the past years, we have met that date pretty reliably.

Mr. DUNN. Thank you. Please get back in writing.

It is my understanding that there are certain circumstances where the period is extended. How long does it take when a sponsor appeals a decision at multiple management levels, so two and three, et cetera?

Dr. MARKS. That can all depend because it depends on how many people are in the chain as it—

Mr. DUNN. Well, I will tell you that in your agency's information it says it takes an average of 211 days if there are two levels, and if there are three levels, it is 256 days. So that begins to become pretty painful.

Next, I want to shift to a few questions regarding the complete response letter and the FDA review documents that are attached to that.

It is my understanding that a CRL basically includes a very brief summary of the deficiencies holding an application back from approval, often leaving the applicant in the dark concerning the reasons the application was deemed deficient.

It is also my understanding that there are generally hundreds of pages of FDA review documents with each CRL, no doubt many hours of work as well, and that information that underlies those CRL letters is not provided to the applicant's sponsor.

Do you think that a sponsor would be better able to resolve their deficiencies more completely and more efficiently if they were

granted access to the full FDA review in addition to the simple CRL?

Dr. MARKS. No, I do not. I think that could be chilling on the effect of our reviewers. Most sponsors actually know quite well what the deficiencies are in their applications before they receive a complete response letter because they have been part of a process which is guided by the user fee commitments in which they have multiple meetings leading up to this, and most often they have been told either at their midcycle meeting or their late cycle meeting of the deficiencies that ultimately lead to their complete response letter.

We could perhaps enhance what we place in the complete——

Mr. DUNN. I will reclaim my time if I may.

They come to our offices, and they tell us just the opposite. They tell us they do not know why they were denied, and they have to go back and dig around and find out what the problem is.

Is it lack of information or is it information that their drug does not work or——

Dr. MARKS. But they are——

Mr. DUNN. We are hearing the exact opposite information from the people who are, you know, applying for these CRLs and paying your user fees.

So honestly, it seems to me the transparency surrounding the FDA review documents makes for a fairer, more efficient process. It is especially helpful to the small and midsize biotech companies, you know, who have the most to lose from a drawn-out process. They cannot survive for a year with no information from the FDA.

You know, importantly, the American patients lose out when these innovative companies have to make decisions based on limited resources, and it chills investors and gives them concern in those companies.

So I want to be sure the agency is working to help the American patients and the innovative companies that are coming before you, both large and small.

Thank you for that.

Madam Chair, I yield back.

Ms. ESHOO. The gentleman yields back.

Thank you for your patience for being here from the very beginning of the hearing.

The Chair is now pleased to recognize the gentlewoman from Michigan, Mrs. Dingell.

Mrs. DINGELL. Thank you, Madam Chair, and to Ranking Member Guthrie, for convening today's hearing.

As my colleagues and our witnesses keep reiterating, timely reauthorization of the FDA User Fee Program is fundamental to ensuring the agency has the resources needed to effectively evaluate product applications and remain the gold standard for the drug approval process worldwide.

Dr. Marks, CBER is responsible for evaluating new and innovative products like cell and gene therapies. These therapies hold great promise for future treatments of a wide variety of diseases and are at the forefront of science.

Dr. Marks, how has the volume of product applications for cell and gene therapies changed since the last user fee authorization?

And how will the policies in PDUFA VII ensure the FDA is able to attract and retain the scientific expertise necessary to evaluate these applications?

Dr. MARKS. Thanks so much for that question.

So over the past five years there has been nearly a doubling in the number of applications. If you look at the number of supplements that have come in, those are amendments to existing investigation of drug applications. They are up over 100 percent during that time, well over 100 percent.

And so we are now at a place where the workload here is tremendous. We are very grateful for the additional resources that the user fee acts have brought to date. This PDUFA VII commitment letter will bring additional resources that are desperately needed to expedite the review of those therapies, and that will be critical to getting these therapies in a timely manner.

We are also though grateful for part of the 21st Century Cures Act, which was the pay authority which allows us to attract outstanding candidates, and that is helping us to move forward attracting talent that we need.

And so, again, the additional provisions of PDUFA VII that will allow us to continue to use the funding for that will be important.

Mrs. DINGELL. Thank you, Dr. Marks.

It is also important that FDA evaluators remain objective and independent while reviewing potential therapies. In fact, as was recently reported, Biogen, the manufacturer of Aduhelm engaged in a lengthy, behind-the-scenes campaign that they researched internally as Project Honest to lobby the FDA for approval of this drug. This allegedly included off-the-book meetings between Biogen and FDA regulators, as well as almost daily working group collaboration between company employees and agency review staff.

FDA's decision to approve Aduhelm is currently being investigated by Congress as well as FDA's Office of the Inspector General, whose report is not due until 2023.

In the interim, Dr. Cavazzoni, what actions has FDA taken to ensure that its regulators are not inappropriately influenced by industry?

Dr. CAVAZZONI. Thank you, Congresswoman.

The decisions that FDA makes are made independently of industry's influence, and this includes the decision that was made on Aduhelm, understanding that there have been allegations and reports in the news.

We have several levels of review of the data. In the instance of Aduhelm, the data were very complex and had even more review within the centers and by experts.

So we agree that it is very important to maintain that independence, as has been the case in past decisions, and that, you know, the PDUFA programs are really allowed to be what they are meant to be, which are ways to have more efficient processes in place and have more staff available to review more applications faster, while upholding our independent decision making and our very high standards.

Mrs. DINGELL. So I have got like 26 seconds. You have told us that you are frustrated here and maybe you can tell us more about that in writing.

But your perspective is helpful. Can you commit that the current rules will not be weakened moving forward so that appropriate guardrails remain with respect to conflicts of interest?

Dr. CAVAZZONI. The guardrails have been in existence and upheld throughout, and we will continue to maintain our high standards and the independence in decision making.

Mrs. DINGELL. Thank you, Madam Chair. I yield back.

Ms. ESHOO. The gentlewoman yields back.

The gentleman from Georgia, Mr. Carter, is recognized.

Mr. CARTER. Thank you, Madam Chair.

And thank all of you for being here today.

Advance manufacturing, which is defined as including both new manufacturing methods and production of new products enabled by innovation, extremely important. It has the potential to dramatically increase efficiency, flexibility, and the quality of production of medicines in this country, and that is extremely important.

It is important for us to be competitive. I have got legislation, Made in America, that we are trying to repatriate companies back to America.

But the innovation is extremely important, extremely important to the future. This type of innovation would allow U.S. manufacturers to be more competitive. It would allow them to increase the resilience of our supply chain, which we know is extremely important, particularly after we have been through this pandemic. And it would, as a result of all of that, ensure our national security.

So to encourage the development of this new technology, as I have said, I have got legislation that would create, you know, a pathway at FDA to assess these manufacturing processes, a policy that is supported by the National Academies of Medicine.

Dr. Marks, I will start with you. Do you agree that the review pathway that is independent of individual drug applications can help bring new manufacturing technology to market?

Dr. MARKS. So without knowing all of the specifics, all I can say that I certainly incredibly support advanced manufacturing technologies, and to the extent that a pathway that helps foster them forward and helps bring our manufacturers here in the United States into the use of these technologies for both drugs and biologics is certainly something we would support, moving products into use of advanced manufacturing technologies.

Again, I am sorry I do not know the details to speak to the exact nature of the review.

Mr. CARTER. But you would support that type of legislation?

Dr. MARKS. What I can say is I am not in a position to support—

Mr. CARTER. I know you have not seen the legislation.

Dr. MARKS [continue]. That we support advanced manufacturing.

Mr. CARTER. OK. Fair enough. Well, it is included in my bill. You need to get familiar with my legislation because it is good, and it includes advanced manufacturing.

Dr. Cavazzoni, what about you? Are you familiar with that as well?

Dr. CAVAZZONI. Well, we are very supportive of advancing technology, and the advanced technologies and expediting the review of these technologies really needs to go hand in hand with the review

of a specific drug and not dissociated from the review of the drug because evaluation of the [audio malfunction] technology is really very much tied to the manufacturing of a specific drug.

And as Dr. Marks has stated, we are really looking forward to build on the gains that we have made in advanced manufacturing, for instance, within CDER. We have approved over, I think, approximately 11 submissions that use the continuous manufacturing, and we see this as an area that we will remain a great focus of ours.

Mr. CARTER. OK. Fair enough. Real quick because I have just a little bit of time left, drug shortages. You know, this is something that we are dealing with, something that we dealt with even pre-pandemic, and it is certainly important.

But APIs, APIs, active pharmaceutical ingredients are extremely important. To what degree does the FDA Office of Drug Shortages and the agency's Inspection and Compliance staff coordinate internally?

Do they work together?

And do they work with manufacturers to make sure that a drug that potentially could be in shortage, to make sure that we can avoid that?

Dr. CAVAZZONI. There is extensive coordination within FDA across multiple groups, and there is also communication and coordination with [audio malfunction] centers, and we have really charged those observations of the supply chain during the pandemic.

But what is very important to be effective in mitigating issues is to have as much up-to-date information as possible for manufacturers as to where these APIs or the finished products are manufactured and how much each facility makes in real time or near real time.

Mr. CARTER. I am out of time, but please make sure we are working with the drug manufacturers when we see these potential drug shortages coming up as well.

Thank you, and I yield back.

Ms. ESHOO. The gentleman yields back, and I appreciate the questions that he has asked.

In the COMPETES Act that you are going to have the opportunity to vote on, I do have language in it that deals with the FDA being able to secure information from manufacturers as to where their drugs are manufactured, if they are outside the country, those that use the API from abroad.

All of that information will be approved to the FDA, which I think is an important step. It does not cure the overall issue, but it is important information that the FDA can gather.

The Chair now recognizes the gentlewoman from California, Ms. Barragán, for her 5 minutes of question.

Ms. BARRAGÁN. Thank you, Chairman Eshoo, for holding this hearing.

Thank you to our panelists.

It sounds a little controversial, but as somebody whose mother is 81 with Alzheimer's, I just want to say I was disturbed by the outcome of the drug only being covered for those in clinical trials,

and I will continue to follow this issue and want to make sure there is equity for access to this drug.

And when you have somebody who has Alzheimer's, you want to be able to have anything available that could possibly help, and so I just wanted to put that out there myself.

My question, my first question is for Dr. Cavazzoni.

Thank you, Doctor, and Dr. Marks for being with us today. Your work on these agreements is critical.

In 2020, generic and biosimilar drugs saved the U.S. healthcare system over \$300 billion in drug spending, and timely approval of the FDA's user fee agreements will ensure patients continue to benefit from lower prescription drug costs.

However, under current law, generics can be blocked from entering the market if safety information on a brand drug's label is protected under exclusivity, but no other hurdles remain.

My bill, the Prompt Approval of Safe Generic Drugs Act, would create a path forward for generic competition in these instances.

Safety information should be a feature of drug labels, not an obstacle to competition. Fortunately, FDA recognizes this problem and the CBO estimates that my bill will save families nearly \$165 million.

Doctor, this is one specific regulatory hurdle that impedes the generic drug review process. Could you discuss how similar regulatory hurdles like this can stifle competition and prevent lower drug prices for consumers?

Dr. CAVAZZONI. Thank you, Congresswoman.

Under the current authorities, we are really constantly looking for ways in which we can facilitate the development of more generics and, therefore, increase competition and lead to lower prices.

We would also be very interested in working with Congress on additional measures that could make us even more efficient, and to that effect, the department has published a drug pricing plan that includes some recommendations for Congress in areas where there could be some legislative changes that would allow us, for instance, to include more information on the branded drug in the label, including inactive ingredients and excipients rather than having the generic manufacturers having to guess what those are because we are barred from telling them.

Another really important potential opportunity are some statutory changes to facilitate the development of hard to make combination products, drug-device combination products, and those are also quite expensive products where we see every opportunity in advancing more generic drugs and creating more competition.

Ms. BARRAGÁN. Thank you.

Dr. Cavazzoni, I am interested in how the agency relies on the use of real-world evidence when making regulatory decisions. It is important that the FDA's regulatory decisions adapt and change as signs change as well.

My understanding is that the prescription drug user fee agreement includes new proposals to review how real-world evidence can be used.

Can you describe the new advancing real world evidence program and what the FDA intends to gain from this kind of program?

Dr. CAVAZZONI. Thank you for that question.

Our ability to utilize the real-world evidence is very much dependent on the quality and the characteristic of the real-world data put against the questions that we are trying to ask, and so we have become very efficient in using real world evidence, for instance, for safety surveillance.

And during the current cycle we have also had a number of demonstration projects to use those data for effectiveness, and so in PDUFA VII we are really looking at additional initiatives to continue to expand the use of real-world evidence for safety, but also, for instance, to support our decision when it comes to new indications for approved products as well as, for instance, used in the Sentinel System to make the pregnancy registries more efficient and easier to conduct for manufacturers.

Ms. BARRAGÁN. Well, thank you for that, and I am over my time. So we probably want to hear about the limitations as well.

Thank you, Madam Chairwoman, and I yield back.

Ms. ESHOO. The gentlewoman yields back.

It is a pleasure to recognize the gentleman from Utah.

Mr. CURTIS. Thank you.

Ms. ESHOO. Mr. Curtis, thank you for your patience. You have been here from the very beginning of the hearing, and you have 5 minutes for your questions.

Mr. CURTIS. Thank you, Madam Chair and Mr. Ranking Member. I am here because this is important.

I am actually one of the few members serving on this committee that has not been through this process before and does not have a healthcare background.

And I am very well aware how important this is, and I have spent a considerable amount of time in the last few weeks with my staff digging in and trying to understand this.

But I also bring a perspective that is different because I have not been here before. I am far away enough from the forest to see the trees. I come from a background of business problem solving and government problem solving.

It is my understanding that this process, as I study this, is about time, access, safe access to medications for patients. I am very well aware of the balance between time and safety and transparent review, and I think Utahans and all Americans deserve a timely and a safe process.

I am very well aware of a number of Utahans who are in difficult positions. One that comes to mind is the mother of a five-year-old whose son is suffering from classic Galactosemia, and this comes with speech delays. He is five years old. It comes with speech delays, learning delays, difficulty with fine motor skills and muscle weakness.

This mother is also aware that there is a drug, AT007, in the process. Every day that drug is not approved is one more day that this child falls further and further behind his peers at a time at five years old when learning is so critical.

And with that in mind, I would like to ask my first question, and I will ask this to both of you.

I have heard a lot of stories like this five-year-old and his mother about Americans who are desperate for access to innovative thera-

peutics, and then we hear today comments like, “Well, we will get back to holding in-person meetings when things get back to normal.”

And you can imagine the frustrations of those waiting for these cures hearing something like that. There is a strong sense that government is not doing everything it can to work on the time aspect of this.

So the both of you I ask: irrespective of this agreement number VII that is before us, what are we doing to accelerate? Why do we need an agreement just to accelerate?

Are we doing our best? And are we more focused on the agreement or on the actual lives that this is impacting?

Dr. CAVAZZONI. I am happy to start, Congressman.

These agreements are really in the end their own issues, and bringing new therapies to patients in areas of unmet medical needs.

And Galactosemia is a really good example of a disease where there are tremendous unmet medical needs.

We can all comment on specific programs because the information is confidential. However, I can tell you that we really work extensively with manufacturers and sponsors to guide them and to accelerate the development and review of these therapies.

And to your point about meetings, in fact, given the incredible increase in workload during the pandemic, our ability to have more nimble meetings, such as teleconferences or video conferences, has allowed us to have more meetings, and this is something that we want to be able to leverage if needed going forward.

So the lack of in-person meetings has in no way slowed us down. If anything, it has allowed us to be more efficient in the face of all this work.

And despite all of this increased volume of work, we have——

Mr. CURTIS. I am going to jump in just because we are so limited on time, and I appreciate your answer.

I think my hope is that with the importance of these agreements we still do not forget the faces and the people behind them that we are trying to serve.

Now, in reference to the agreements, I understand that a lot of our goals related to the FDA review process and timeliness, but also include initiatives that are part of the Center for Drug Evaluation Research.

I believe American innovation is extremely important in what we do. I would like to ask what initiatives are the FDA intending to prioritize and how will you properly implement these initiatives?

Dr. CAVAZZONI. We could not agree more continuing to serving the baseline. When we look at a commitment letter, our intention is to meet all of the new goals and commitments and as we have done in the past, and we are obviously going to need some additional resources to do so which is also [audio malfunction] in your proposal.

Mr. CURTIS. I am out of time. Madam Chair, I yield the balance of my time.

Ms. ESHOO. The gentleman yields back.

Let me just state the following so that members that are meeting with us virtually as well as those who are in the hearing room

know. We are going to continue on until about 25 after one. I know members on both sides of the aisle want to attend the classified briefing.

So hopefully we be able to have the second panel give their testimony, and then we will break for the classified hearing, and then resume at what, hopefully 2:30.

And then there is an expectation of a series of votes beginning at either 4:00 or 4:30, but we want to conclude our work.

So be advised, all of the members.

The Chair is now pleased to recognize the gentlewoman from Illinois, Ms. Kelly, for her 5 minutes .

Ms. KELLY. Thank you, Madam Chair and Ranking Member Guthrie, for holding this hearing on the FDA user fee authorizations.

According to the National Institutes of Health, clinical trials for cancer treatment funded in fiscal year 2018 had a median participation of 80 percent White participants, only five percent Black, and three percent Hispanic participants.

This is one of the many examples underscoring the need for clinical trials to reflect the disproportionate impact these conditions have on communities of color.

Given the very low rates of racially and ethnically diverse participants in clinical trials, I was disappointed to see that the Prescription Drug User Fee Agreement VII commitment letter refers to clinical trial diversity only once.

However, I applaud the agency's work in trying to use digital health tools to improve clinical trial diversity.

Dr. Cavazzoni, how will FDA and industry address some of the barriers to accessing digital health tools, such as the lack of digital literacy or lack of English proficiency?

Dr. CAVAZZONI. Thank you, Congresswoman.

We could not agree more as to the importance of increasing diversity in clinical trials. As you mentioned, the commitment letter includes some enhancements around digital health technology, and we are doing a lot more beyond that.

We have issued guidance on how to enhance clinical trial diversity. We are going to continue to track also progress very closely by issuing periodic reports showing the data on the clinical trial enrollment and diversity in clinical trials in the various therapeutic areas.

And we want to continue to work with the sponsors to encourage them to the full extent of our current authorities to have diversity in clinical trials.

Understanding that the results were balanced, so we struck depending on therapeutic areas or the type of clinical trials, and so we need to also be aware of that and making sure that we make the clinical trials more diverse while also finding ways to continue to conduct them in a timely manner.

One of the important elements will be to also have more access to healthcare for underserved community, which tends to track also with access to investigative sites and outposts of clinical trials so that we can enroll diverse populations.

Ms. KELLY. Also on December 2018, FDA released their framework for FDA's Real World Evidence Program and stated a commit-

ment to using real world evidence to bolster data in clinical trials, specifically in populations that were not studied prior to drug approval.

And I am glad to see FDA's continued commitment to real world evidence reflected in the user fee agreement.

So I also wanted to ask you what steps is FDA taking to leverage real world evidence in determining how a drug works in populations that were not studied prior to approval, such as racially and ethnically diverse communities.

Dr. CAVAZZONI. Thank you for the question.

This is a big part of our program, and we are looking forward to expanding it in PDUFA VII. Real world evidence can be used to understand the natural history of disease, to understand the characteristics of specific populations, including ethnic and racial minorities.

And it can also be used as an incremental or additional evidence when it comes to complement clinical trial information that would arise from clinical trials.

And to that effect the commitment letter includes a number of enhancements that would allow us to better understand the quality of real-world data and to hopefully put it to work to answer more questions, including questions about effectiveness of drugs.

Ms. KELLY. Thank you so much.

Thank you, Madam Chair, and I yield back.

Ms. ESHOO. The gentlewoman yields back.

It is a pleasure to recognize the gentleman from Pennsylvania, Dr. Joyce, for your 5 minutes of questions.

Mr. JOYCE. Thank you for yielding, Madam Chair Eshoo.

Briefly to touch on the iPLEDGE REMS matter again, on December 23rd, 2021, the FDA stated that it is ready to exercise regulatory flexibility on a temporary basis with regard to certain requirements of the iPLEDGE REMS provided that Isotretinoin Project Manufacturers Group proposes a workable solution that ensures the necessary safe use conditions.

Right now because regulatory flexibility has not been exercised, many patients have not been able to receive their Isotretinoin. It is estimated to be in the thousands.

This is a life changing medication. I know that because I prescribed it for 25 years.

Dr. Cavazzoni or Dr. Marks, would you please describe first what this regulatory flexibility will look like and, more important, why has the FDA not exercised this regulatory flexibility over the past six weeks?

Dr. CAVAZZONI. Thank you for that question. I am happy to address it since the Accutane is regulated by us.

So manufacturers are responsible for the implementation of grants, and in this situation, the manufacturers had to make a transition to new platforms to deliver the REMS, which caused significant challenges for prescribers, pharmacies, and patients.

And we have been working with those groups since before the [audio malfunction] and since the transition, and we really empathize with this [audio malfunction].

We have had conversations with the manufacturers and the various stakeholder groups, and, yes, we have indicated openness to

make some adjustments, temporary adjustments, to the REMS to facilitate the transition.

Ultimately, it is up to manufacturers to determine whether they are willing to make those changes or whether those adjustments are realistic to make without taking even more time to solve the problems in the platform.

So we know that this has been a really long road for prescribers, pharmacists, and patients. The good news is that we seem to be turning the corner, and if we look at the number of prescriptions that are currently issued, we are seeing a return to the historical baseline level of prescriptions before this transition that took place in December.

Mr. JOYCE. Do you feel that the necessary regulatory flexibility is in place?

Dr. CAVAZZONI. As I said, we indicated our willingness to exercise some flexibility. Ultimately it is up to the sponsors to take our recommendations or suggestions into consideration and determine whether it is practically or operationally feasible to make those temporary adjustments where we would be able to—

Mr. JOYCE. My time is limited. Has the FDA offered those recommendations?

Dr. CAVAZZONI. We have discussed those recommendations and, as I said, it is up to the sponsor to determine whether they can be implemented.

Mr. JOYCE. Thank you.

I know patients are suffering without access to complete the 20-week course of Accutane. This ability, as I mentioned, is lifechanging as far as a medical therapy.

In the brief time that I have remaining, according to FDA reports from November of 2021 on inspection oversight, there are 60 applications that are delayed right now due to the inability to conduct inspections or facility assessments as of September 30th.

How long will it take to address this backlog, please?

Dr. CAVAZZONI. Thank you, Congressman.

While we have authority to use alternative approaches to inspections to the fullest extent, and while we have intention to conduct mission critical inspections, there are some instances where we need to be able to [audio malfunction] with boots on the ground.

And what has [audio malfunction] us right now are still some travel challenges, quarantines, and so we will resume inspections, those inspections, as soon as the overall conditions will allow us to do so.

Mr. JOYCE. With the widespread availability of vaccine, when do you expect that return to normal operations for inspections to occur?

Thank you. My time has expired, and I yield.

Ms. ESHOO. I think that that question—

Mr. JOYCE. We will submit the question. Thank you.

Ms. ESHOO [continue]. Will be submitted for a written response. Certainly.

The Chair is pleased to recognize the gentlewoman from New Hampshire, Ms. Kuster, for her 5 minutes of questions, followed by, I think, Dr. Schrier unless there are others from the Republican side, followed by Mrs. Trahan.

Ms. KUSTER. Thank you very much, Madam Chair.

Ms. ESHOO. Ms. Kuster of New Hampshire, yes.

Ms. KUSTER. Thank you.

And I apologize for losing my turn. We were evacuated from the Cannon Building.

I want to thank the witnesses from the FDA for being with us, and I am going to jump right in in the interest of time.

On September 9th last year, the administration released a report titled "Comprehensive plan for addressing high drug prices." This report included several administration proposals on drug pricing, but the issue I want to discuss was related to accelerating the development and approval of lower cost drugs.

In this report, the administration said Congress should clarify that it is not an improper disclosure by the FDA to provide a potential generic drug sponsor with the names and amounts of inactive ingredients used in the formulation of a reference listed drug when a generic drug is required to have the same formulation to obtain approval.

It is my understanding that the limited guidance FDA currently provides to generic drug applicants and their proposed drug formulation can significantly delay the approval of complex lower cost drugs.

As this committee considers opportunities to address barriers to patient access to affordable therapies, this seems like a policy worth considering in the user fee package.

Dr. Cavazzoni, does the FDA still consider the type of feedback they provide to generic applicants a barrier to generic drug development and patient access to lower cost medicine?

Dr. CAVAZZONI. Thank you, Congresswoman.

The current constraints that we have in our ability to share information with the generic manufacturers when it comes to inactive ingredients and excipients is one of the areas that makes the development of complex generics less efficient than it should be.

And to that effect, the administration has issued these suggestions or recommendation to Congress, and we think that the inclusion of excipient and inactive ingredient information in the brand label would go a long way in facilitating the development of complex generics.

Ms. KUSTER. Thank you. You anticipated my question, what legislative policies are that we should consider. So we will take your response under advisement as we are drafting the legislation.

I want to go forward now, switching gears, to look for Dr. Marks, how the FDA is committing to keeping patient perspectives in mind. I reviewed the FDA's PDUFA VII commitment letter, and I was pleased to see a public meeting on patient-focused drug development.

Dr. Marks, when the FDA reviews cell and gene therapies, for example, for diseases like Type 1 diabetes, how does the FDA currently evaluate patient perspective data?

And I will just jump right in with the second half. Can you commit to me that the FDA will make sure the patient perspectives are a focus area as the agency enhances the cell and gene therapy program in PDUFA VII?

Dr. MARKS. Thanks so much for that question.

Indeed, we are very much involved in trying to get patient perspective. There are multiple guidances to help develop patient perspectives, and we are very interested in making sure that we have an appropriate number of meetings with a variety of different patient groups on a variety of different topics.

Some of them are larger, more formal. Some of them are smaller and less formal. They provide invaluable information about what patients really need from the products that are being developed in terms of how they feel, function, or survive.

I can at least commit to the fact that we will certainly continue to incorporate this, as we move forward and work with sponsors and consider these approvals ourselves.

Ms. KUSTER. Thank you.

And just to wrap up, my focus in this committee is both on lower cost and access to prescription medication and devices for patients and the patient perspective. I think those are the two goals that I think many of my colleagues share.

I will just say my husband picked up my monthly asthma medication and came home and it was \$182, and people are really struggling, and you are doing an amazing job to bring such amazing treatments and therapies, but we have got to do our best to lower the cost and meet the patient's needs.

So thank you, and I yield back, Madam Chair.

Ms. ESHOO. Amen, and the gentlewoman yields back.

The Chair is pleased to recognize the gentlewoman from Washington, the State of Washington, Dr. Schrier.

Ms. SCHRIER. Thank you, Madam Chair.

Thank you, Dr. Marks and Dr. Cavazzoni, for taking the time to be here today, and thank you for your continued hard work to keep Americans safe and educated during this crisis. So thank you for your service.

Also, thank you to my colleagues for really interesting questions to listen to.

As a physician myself and a person with Type 1 diabetes, I am sure you can imagine how close to home insulin and insulin pricing and the development of biosimilar insulins really hits for me.

And I was really honored to work with Representative DeGette and other members of the Diabetes Caucus in the 116th Congress to clarify and expedite a biosimilar approval pathway.

And I was really pleased to see the approval of the first interchangeable biosimilar insulin just last summer. So I am eager to hear today about some of the regulatory science enhancements that will be in PDUFA.

And first, Dr. Cavazzoni, just a little timeline here. As you know, the Biologics Price Competition and Innovation Act was enacted as part of the Affordable Care Act in 2010, and yet, as mentioned, the first biosimilar insulin was just approved this summer. There is an 11-year gap.

And now there are plans in this next authorization to have a demonstration project to advance interchangeables starting in fiscal year 2023.

And I am just wondering what you see as a time frame. Why did it take ten years and what should be expect with these new projects?

Dr. CAVAZZONI. Thank you for the question.

And we agree that the approval of the first interchangeable insulin was a landmark approval for the program.

The program is relatively new and has had to, you know, get on its feet in the first cycle, as all programs.

If we look at the achievements for this current program, they have been truly remarkable. We have gone from five to 33 biosimilars that are approved, and we are talking in the BsUFA III proposal to have enhancements to facilitate additional indications for these approved biosimilars.

We also have a very rich pipeline of biosimilars in development, and so we think that this momentum is going to continue and that we are going to see faster results.

In particular, thanks to this new pilot program that will allow us to do applied regulatory research to solve those problems that have sort of made it more difficult to develop biosimilars, but even more importantly, to develop interchangeable biosimilars.

Ms. SCHRIER. Thank you.

And thank you for pointing out that there have been so many. As I look at the list and I hear you talk about these 33, I do not know if the general public knows that some of the most expensive medications like Humira is on that list as now having a biosimilar, and that is, you know, theoretically lifechanging for a lot of people out there.

Kind of on that theme, the generic insulin that I referred to before is still pretty darn expensive, and when I think of biosimilars, I think of biosimilars kind of like generics, and in some cases those generics have met a significant price drop for the consumer, but that is not always the case.

And so, you know, this generic insulin or biosimilar insulin is still pretty expensive. I do not know how the biosimilar Humira is and Neulasta, comparing with price.

I was wondering if you could comment on that. You know, for the everyday American who is looking forward to having these, what can they expect in terms of cost and availability?

Dr. CAVAZZONI. Congresswoman, it is a top priority to make lower cost drugs accessible to all Americans, and while FDA does not have a role in setting prices or negotiating prices, we do have a role in increasing competition.

And the way in which we can increase competition which has the potential and as shown with generics to lower prices is to approve more biosimilars and approve more interchangeable biosimilars.

And so we think that this program, which we have, thanks to Congress, has and really shows the wisdom of Congress establishing this program, will really yield increasing results for the American public in lowering prices.

Ms. SCHRIER. Well, thank you very much.

And I yield back.

Ms. ESHOO. The gentlewoman yields back.

The Chair is pleased to recognize the gentlewoman from Minnesota, Ms. Craig, for her 5 minutes of questions.

Ms. CRAIG. Well, thank you so much, Chairwoman Eshoo, and thank you for holding this incredibly important hearing today for us.

As a member of Congress, one of my top priorities is expanding my constituents' access to lifesaving prevention, treatments, and cures at affordable cost.

One of the issues I hear most often from my constituents is the ever-rising cost of prescription drugs. Policies like PDUFA, the generic drug user fee agreement, play a critical role in ensuring that lower cost generic alternatives can reach more patients more quickly.

Since 2012, GDUFA has provided FDA with the resources it needs to shorten approval times and clear the backlog of generic drug applications. GDUFA III builds on ongoing efforts to increase product-specific guidance and communication between FDA and industry for the specific benefit of patients.

My questions today focus primarily on complex generics which have faced unique barriers and carry significant potential to improve patients' lives.

Dr. Cavazzoni, we know that complex generics like epinephrine auto injectors or inhalers are more difficult for manufacturers to develop. They are also more challenging for FDA to evaluate.

In your experience, why is it so difficult to get complex generics developed and approved?

Dr. CAVAZZONI. Well, there is an inherent, you know, greater degree of difficulties in these generics because of the type of formulation or because, to your point, they may include a device and a drug combination and route of administration, and so on.

And so it is more complicated to find ways to establish that those complex generics are bioequivalent to the brand, which is the standard that we need to use.

And there is also in many instances need to actually study new methods to determine that bioequivalence. And so one of the very important elements of GDUFA currently is a very successful research program that has really focused on how we can find new analytical methods to establish bioequivalence and spur the development of complex generics.

I echo also your point about the importance of product-specific guidances, and the GDUFA proposal includes new performance goals to issue product-specific guidance for these complex generic products so that we give clarity to developers on how to develop them.

Ms. CRAIG. You actually touched on my second question there in your answer here. When you talk about product-specific guidance, can you give us an example or examples of how that will help developers and enable them to get those products to patients much more quickly?

Dr. CAVAZZONI. Yes. An example, these product-specific guidances are a bit like a "how to" guide and guide manufacturers on how to establish the parameters that would allow us to determine that the drug is the same as the brand drug.

They also clarify our expectations when it comes to those parameters and the methods to which we would expect them to conduct those analyses.

And so they are really somewhat of a recipe book, and it is much easier to have a recipe book than having to do trial and error when it comes to making anything, including drugs.

Ms. CRAIG. Well, thank you so much, Dr. Cavazzoni.

I really do look forward to my colleagues and I coming together in hopefully a bipartisan fashion to support an expedient and fair user fee reauthorization process.

I know that FDA's ability to make sure that patients can gain access to safe and effective products absolutely depends on it.

So thank you so much.

And, Madam Chair, I yield my time.

Ms. ESHOO. The gentlewoman yields back.

The Chair is pleased to recognize the gentleman from California, Dr. Ruiz, for his 5 minutes of questions.

Mr. RUIZ. Thank you, and thank you all for being here to testify today.

As we all know, there is a severe lack of appropriate diversity in clinical trials, which leads to under-sampling of large populations and incomplete data. That means that we might not know how effective a drug is on certain patient populations, and patients that are underrepresented in clinical trials may be taking medications that are not effective for them, potentially leading to worse health outcomes.

As a doctor who both grew up and served in a community that is very extremely underserved, I know firsthand the many barriers that exist for individuals who may want to participate in a clinical trial. Those barriers include traveling long distances, the lack of transportation, inflexibility of work schedules, and inflexible work schedules and limited financial resources needed to participate, just to name a few.

So it occurs that the prescription drug user fee agreement commitment letter includes expanding the use of decentralized clinical trials, which is an important step to addressing some of those barriers.

Ultimately, this will help increase trial participation by allowing patients to get some of their care virtually.

Dr. Cavazzoni, is there a plan on how the FDA will expand the use of decentralized clinical trials?

And if so, can you share that plan?

Dr. CAVAZZONI. Thank you, Congressman.

It is very much our intention to continue to promote and expand the use of decentralized trials. We have really learned a lot about decentralized trials during the pandemic. We have actually issued guidance clarifying for manufacturers that they should really try to adopt those approaches to the fullest extent possible.

And we are going to take what we have learned during the pandemic and use it to develop guidance, go-forward guidance, not tied to the public health emergency, to continue to make those trials easier to conduct, when appropriate.

Mr. RUIZ. Thank you.

While decentralized trials can broaden access, we also know that not everyone may have the necessary equipment for such visits. So I introduced the DIVERSE Trials Act, which creates safe harbors for sponsors to supply patients and trials with tech-like tablets that they would need to do remote care, for example.

We also know that the reality for many clinical trials like cancer treatment is that a patient will still have to physically come into the office for procedures like surgery or chemo infusion.

So that puts us back into the access issue for folks who live further from academic centers or have limited means or flexibility.

So the DIVERSE Trials Act will ensure that clinical trial sponsors can provide financial assistance to patients to cover nonmedical costs like travel or lodging related to a trial visit.

So while I realize that these provisions are outside of the FDA's jurisdiction, I do want to raise the issue that there are additional barriers to address to create greater access and diversity and participation.

So given that, Dr. Cavazzoni, in addition to decentralized clinical trials, what additional concrete steps can the FDA take to help further the use of alternatives to standard clinical trials and effectively get lifesaving drugs into the hands of patients more quickly, safely, and equitably?

Dr. CAVAZZONI. We have a number of tools at our disposal. First, we strive to work with manufacturers and sponsors to make sure that clinical trials do not have sort of a whole bunch of added things that are not really essential and just make everyone's life more complicated, including the patient's, because they usually entail more visits, and so on. So trying to make trials efficient is very important.

The use of digital health technologies is really important, and access to those technologies, to your point, is very important because they can really make taking a consent from a patient much easier and save a visit and just do it like we are doing it today, individual conference.

What we also want to promote as far as decentralized clinical trials is the trial going to the patient. So the nurse, for instance, going to the patient to administer the drug or to take a measure, and so on, recognizing that in order to have more diversity in clinical trials we need to make it easier for patients to be able to participate.

And not all patients have the luxury of being able to trek across town three times a week to be able to participate in a clinical trial.

Mr. RUIZ. Thank you very much.

I yield back my time.

Ms. ESHOO. The gentleman yields back.

The Chair recognizes the gentlewoman from Massachusetts, Mrs. Trahan, for your 5 minutes of questions.

Mrs. TRAHAN. Thank you, Madam Chair.

And thank you to the witnesses here today to discuss FDA user fees with our subcommittee.

FDA's mission is to protect and promote the public health in the country, and FDA user fees are essential to these efforts.

In FDA's testimony, the agency says that over the past two years, FDA has continued to work at a pace that is unprecedented and not sustainable outside of an emergency to deliver authorized and approved therapeutics and vaccines with unparalleled speed to meet critical public health needs.

Through COVID-19, FDA has been critical in the approval of vaccines and therapeutics to see our Nation through this crisis. The

infrastructure and capacity to review applications so rapidly is due in large part to the funding from these user fees.

So, Dr. Marks, how does PDUFA VII reflect the lessons learned through the COVID-19 pandemic?

And if you could, also touch on any pandemic preparedness measures in PDUFA VII.

Dr. MARKS. Thanks. Thanks very much.

I think one of the key pieces that is essentially put in place here are some of the enhancements to meetings. Again, I know it sounds very boring, but that early input that sponsors can get, the interact meetings provisions that are now put into the commitment letter will help sponsors get early, relatively informal regulatory advice that will hopefully set them on the right track towards the development of their product.

If they do not make mistakes and waste time and money early on in development, they are able to move forward more quickly.

It also sets them up and establishes them with a relationship with the agency early on in their development program to interact with our reviewers.

So I think that is just one example. There is also the Type C meeting, which is a very specific type of meeting around one or two issues that will hopefully allow people to get resolution more quickly in this.

So those, I think, will be very helpful moving forward as we go ahead. I think those also will help us, for that matter, in terms of pandemic preparedness because we have had any number of very innovative products come in early on looking to try to address potential hazards in the future.

Mrs. TRAHAN. Great. I appreciate that. It is not boring to us. So thank you for that.

So prescription drug user fees were first passed due to lessons learned from the HIV/AIDS epidemic. As the agency and this subcommittee are fully aware, another epidemic the Nation continues to grapple with is the ongoing opioid and overdose crisis.

From April 2020 to April 2021, we lost over 100,000 Americans to an overdose, and that is just a staggering number.

Dr. Marks, I am wondering how does PDUFA VII reflect these unprecedented deaths in this ongoing crisis, and will PDUFA VII allow for expedited review of OUD treatments and opioid antagonist medications that are in the pipeline?

Dr. MARKS. So I really appreciate the question, which I am going to turn over to Dr. Cavazzoni because her center handles that.

We have a few very creative and innovative treatments, such as vaccines, for opioid addiction that are in the pipelines, but I will turn it over to her.

Dr. CAVAZZONI. Yes, thank you, Congresswoman, and we recognize the tragedies of the opioid epidemic, and within our center we are looking at all the aspects of our authorities right now to see whether we can do more and where we can sort of double down.

When it comes to development of treatments for opioid use disorder or medication assistant treatments, the answer is, yes, absolutely. All of the expedited pathways that we currently have in PDUFA and all of the enhancements that we are or many of the

enhancements that we have in PDUFA VII will apply also to accelerating the development of opioid use disorder treatment.

And I would add to that also hopefully the development of non-addictive pain medications that may be able to replace or decrease the use of opioids for pain conditions.

Mrs. TRAHAN. Great. I appreciate your thorough answers.

I have one more question, but given the time, I am going to submit it for the record, and thanks again for being here and lending your expertise at this important hearing.

Thank you.

Ms. ESHOO. The lovely gentlewoman has completed.

We have Representative Schakowsky, a member of the full committee but not ours, and so she is waiving on. I recognize her for 5 minutes.

And I should say that on the heels of Ms. Schakowsky questioning, we will recess so that the next panel of witnesses can get some lunch and the members of our committee are able to attend the classified briefing, which is important to all of us, and we will resume at 2:30.

So, Ms. Schakowsky, you are recognized for 5 minutes.

Ms. SCHAKOWSKY. Well, thank you once again, Madam Chair, for allowing me to waive onto this important committee.

You know, I am happy to meet with the Food and Drug Administration, which really does have a mission to make sure that the drugs, including biologics, are safe and effective.

But I am very, very concerned that recently we have seen a wavering of that commitment to do that, and I am talking about what happened recently with the Biogen's Alzheimer's drug, Aduhelm, and I just feel like this has been very scandalous.

This is a drug that at first, initially, you said that would not be approved at all and now it has been on accelerated approval. And this drug was only tested on people with mild Alzheimer's and dementia, but yet the FDA approved the first label to be for all Alzheimer's patients, holding on the hope that this was good for all of them.

And, you know, there have been reports from the limited trial that was done of severe harms, including brain bleeding and other serious harm, and actually there were people, I understand, that even died, and it excluded in that limited trial that was done before the accelerated approval; it eliminated people who had other diseases.

I am sorry. If you have Alzheimer's disease, many people of that age have many other complicating diseases. But those people were excluded.

And all [audio malfunction] independent advisory group. These are the experts that you had in the field who said that this should have been approved. Ten of them actually said, no, this drug should not be approved. One of them did not vote or, you know, abstained.

And it is just outrageous. Three of those advisors actually resigned from the committee.

So Dr.—I am sorry—Dr. Cavazzoni, and, Dr. Marks, if you want to respond at all, how did this happen?

You know, this is also a drug that they said the price was going to be \$56,000 per person per year. I know that that price is unlimited, and I know that CMS is looking at other ways, but I want to really understand how such a thing has happened.

Dr. CAVAZZONI. Thank you, Congresswoman.

There are a lot of aspects to your question, and I will try to address as much as I can in the very limited time we have, and we will be happy to follow up with your staff to address the rest.

What I can say is that the data for this application was very complex. We brought it to the Advisory Committee. We heard very loud and clear from the Advisory Committee that they believed that the data did not support a traditional approval.

We took that to heart. We went back and did more analysis of the data and—

Ms. SCHAKOWSKY. Excuse me. You say you took it to heart. All of the members, none of them said that they supported it. Ten said no. Three resigned as a result. One said this was the worst thing he had ever seen. So do not tell me that you took it to heart.

I do not understand what you are saying.

Dr. CAVAZZONI. Well, in fact, we did because we agreed with the Advisory Committee that the data did not support traditional approval.

We did conclude after looking at the data even more extensively that it supported using accelerated approval based on a surrogate biomarker, an amyloid decrease reasonably predicting the clinical benefit of the drug.

So in fact, we did—

Ms. SCHAKOWSKY. Who approved—

Dr. CAVAZZONI [continue]. Agree with the Advisory Committee on—

Ms. SCHAKOWSKY. My time has expired, but you know, I simply want to say to you that I think this—

Ms. ESHOO. The gentlewoman's time has expired. The gentlewoman's time has expired, and I believe you can—

Ms. SCHAKOWSKY. Let me just say—

Ms. ESHOO. [continue]. And I believe that you can—

Ms. SCHAKOWSKY [continue]. Look in this committee—

Ms. ESHOO. You can submit—

Ms. SCHAKOWSKY [continue]. Accelerated approval. You need to look at accelerated approval and how that works.

Thank you.

Ms. ESHOO. All right. Well, the gentlewoman's time has expired. The Chair is now going to call a recess.

We want to thank both of our witnesses, Dr. Marks and Dr. Cavazzoni. It has been a long hearing for you, but we want to thank you for your testimony, for answering the questions, and for the questions that will be submitted to you in writing.

So on behalf of all of the committee, we thank you. We thank you.

To the second panel, we will resume at 2:30.

So we are now in recess.

[Recess.]

Ms. ESHOO. The Subcommittee on Health will now come back to order.

I want to welcome our witnesses that are part of this second panel, each one distinguished in their own way.

Dr. Lucy—now, let me see if I can get your name right and pronounce it correctly—Vereshchagina; is that correct? Is it correct?

Dr. VERESHCHAGINA. You bet.

Ms. ESHOO. Oh, good. She is the Vice President of Science and Regulatory Advocacy at PhRMA, the Pharmaceutical Research and Manufacturers. Welcome and thank you, especially for your patience today.

Dr. Cartier Esham; is that correct? A little bit beginning of my name. So I got the first syllable correct.

She is the Chief Scientific Officer and Executive Vice President of Emerging Companies at the Biotechnology Innovation Organization and our abbreviation of that, of course, is BIO. Welcome to you and thank you.

To Juliana Reed. How is Juliana—

Ms. REED. I am here. I am here, Chairwoman. I am virtual today.

Ms. ESHOO. OK. Well, welcome to you, Juliana.

Juliana is the Executive Director of the Biosimilars Forum. So thank you for joining us and being willing to be a witness.

And David Gaugh. He is the—welcome—the Senior Vice President of Science and Regulatory Affairs at the Association for Accessible Medicines, AAM.

And Dr. Reshma Ramachandran, correct? Thank you.

And she is a Physician-Fellow at the Yale National Clinician Scholars Program, and the Chair of the FDA Task Force at Doctors for America.

Thank you for joining us and for being willing to be a witness at this important hearing.

So we will begin with Dr. Vereshchagina for 5 minutes of your testimony.

STATEMENT OF LUCY VERESHCHAGINA, Ph.D., VICE PRESIDENT, SCIENCE AND REGULATORY ADVOCACY, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA; CARTIER ESHAM, Ph.D., CHIEF SCIENTIFIC OFFICER, EXECUTIVE VICE PRESIDENT, EMERGING COMPANIES, BIOTECHNOLOGY INNOVATION ORGANIZATION; JULIANA M. REED, EXECUTIVE DIRECTOR, BIOSIMILARS FORUM; DAVID GAUGH, SENIOR VICE PRESIDENT, SCIENCE AND REGULATORY AFFAIRS, ASSOCIATION FOR ACCESSIBLE MEDICINES; AND RESHMA RAMACHANDRAN, M.D., PHYSICIAN-FELLOW, YALE NATIONAL CLINICIAN SCHOLARS PROGRAM CHAIR, DOCTORS FOR AMERICA FDA TASK FORCE

STATEMENT OF LUCY VERESHCHAGINA, Ph.D.

Dr. VERESHCHAGINA. Good afternoon, Chairwoman Eshoo, Ranking Member Guthrie, and the members of the subcommittee.

My name is Lucy Vereshchagina, Vice President, Science and Regulatory Advocacy at the Pharmaceutical Research and Manufacturers of America, or PhRMA.

PhRMA represents the country's leading innovative biopharmaceutical research company which is devoted to discovering and developing——

Ms. ESHOO. I think, Doctor, if you could bring your microphone even closer. You have a soft voice, and we do not want to miss anything you are saying.

Dr. VERESHCHAGINA [continue]. That enable patients to live longer, healthier, and more productive lives.

I am pleased to appear before you to provide PhRMA's perspective on the importance of the Prescription Drug User Fee Act, PDUFA, and the Biosimilars User Fee Act, BsUFA, and their timely reauthorization.

Today I will briefly speak to PhRMA's perspective on the success of the two user fee programs and key elements of each agreement.

For nearly 30 years, PDUFA has helped the FDA fulfill its central mission, to help protect and promote public health by allowing the agency to keep pace with ever-evolving science and have the resources to review innovative drugs and biologics.

In large part, because of PDUFA and the biopharmaceutical system, the United States now leads the world in the introduction of new medicines, and FDA's human drug review program is the global gold standard for regulatory review and approval.

The PDUFA program has produced five different tangible results that matter to patients. Since 1992 when the program was first enacted, PDUFA has provided timely patient access to more than 1,700 new drugs and biologics.

The uncertainties of COVID-19 have highlighted the importance of the economic competitiveness of our Nation and the need for continued advancement of the innovation-based industries.

PDUFA VII efforts built on the program's past successes and are aimed at modernizing the FDA's regulatory and drug development paradigms, stressing as they increased co-capabilities and improving issues in drug review.

Increased regulatory predictability encourages continued significant investment in research and development made by pharmaceutical companies in the United States. The continued number of approvals occurring despite COVID-19 pandemic is a testament to the agency's ongoing commitment to the public health and dedication of biopharmaceutical companies to drive medical advancement.

PDUFA VII also addresses new areas such as advancing digital health technologies, supporting a new wave of advanced biological therapies, such as cell and gene therapies, and enhancing innovation in manufacturing and product [inaudible] areas.

PDUFA VII will advance new and powerful tools, including new clinical trial design, digital health technologies, and real-world evidence that will harness scientific advances, expedite drug development, and ultimately increase patient access to new therapies.

PDUFA VII will also enhance patient-centric drug review with the use of patient preference information and enhancement to monitoring, including for pregnant women.

PDUFA VII also includes commitment that advanced COVID-19 lessons learned and enhance our future preparedness in the ability to keep pace with scientific advancements, including the broader

use of these technologies during a pandemic that has enormous positive impact on the conduct of clinical trials.

Digital health technologies including artificial intelligence enable conduct of remote or distant [inaudible] clinical trials that can enable more diverse patient populations to participate.

PDUFA VII will also ensure FDA's backing resourcing in the infrastructure and be able to support increasing drug review and approval, modernize the basic infrastructure, including adapting cloud-based technologies and enhance pf the financial and staff resource management by promoting contribution transparency.

So with these targeted improvements, PDUFA VII will have a lasting and meaningful impact on the biopharmaceutical industry and basically developing [inaudible] safe and effective medicines for patients in a timely manner.

I will now briefly turn to BsUFA. Biosimilars are playing an increasingly critical role in bringing new options to patients. And BsUFA has been essential for FDA's ability to review biosimilar products and has resulted in 33 approved biosimilar products to date, including two interchangeable products.

And BsUFA III will build on the program's success and enhance the development and review of both biosimilar and interchangeable biosimilar products while ensuring stability and continued maturation of the program.

In conclusion, it is imperative that there be the ability to help us deliver new treatments and cures to meet patients' medical needs. PDUFA VII and BsUFA III will help ensure that patients have timely access to vaccines and medicines while maintaining the United States global leadership in biopharmaceutical innovation.

PhRMA and its member companies strongly support PDUFA VII and BsUFA III and are committed to working closely with FDA and all stakeholders to ensure the continued success of these programs.

And PhRMA, therefore, urges Congress to reauthorize PDUFA and BsUFA in a timely manner to protect against any disruption to this critical program.

And we look forward to continuing to work with the committee, members of Congress, and other stakeholders on these important issues.

Thank you for the opportunity to provide this testimony, and I will be happy to address any questions.

[The prepared statement of Dr. Vereshchagina follows:]

Testimony of

Lucy Vereshchagina, PhD, Vice President, Science and Regulatory Advocacy
Pharmaceutical Research and Manufacturers of America (PhRMA)

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

**Hearing on “FDA USER FEE REAUTHORIZATION: ENSURING SAFE AND
EFFECTIVE DRUGS AND BIOLOGICS”**

February 3, 2022

Good afternoon, Chairwoman Eshoo, Ranking Member Guthrie, and the Members of the Subcommittee:

My name is Lucy Vereshchagina, Vice President, Science and Regulatory Advocacy at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Over the past 20 years, PhRMA member companies have invested more than \$1 trillion in the search for new treatments and cures, including an estimated \$91.1 billion in 2020 alone.ⁱ

I am pleased to appear before you to provide PhRMA's perspective on the importance of the Prescription Drug User Fee Act (PDUFA) and the Biosimilar User Fee Act (BsUFA) and their timely reauthorization. As you know, PhRMA served as one of Industry's principal negotiators with FDA and fully supports both the PDUFA VII and BsUFA III technical agreements.

Today, I will briefly speak to PhRMA's perspective on the successes of the two user fee programs and key elements of each agreement.

Perspectives on the Success of the PDUFA Program

For nearly 30 years, PDUFA has helped the FDA fulfill its central mission – to help protect and promote the public health – by allowing the Agency to stay abreast of ever-evolving science and have the resources to keep pace with the innovative drugs and biologics entering the review pipeline.

In large part because of PDUFA, the United States now leads the world in the introduction of new medicines,ⁱⁱ and the FDA's human drug review program is the global gold standard for regulatory review and approval. Over the years, the PDUFA program has produced positive and tangible results that matter to patients. Since 1992 when the program was first enacted, PDUFA has provided more timely patient access to more than 1,700 new drugs and biologics including treatments for cancer, rare diseases, cardiovascular, neurological, and infectious diseases.

The uncertainty of the global pandemic has highlighted the paramount importance of the economic competitiveness of our nation and the need for continued advancement of innovation-based industries. PDUFA VII will build on the Program's past successes to bolster critical capabilities, improve efficiencies in drug review, and encourage the significant R&D investments made by biopharmaceutical companies in the United States.

PDUFA plays a critical role in the FDA's ability to review human drug applications. Consequently, the Program also provides biopharmaceutical companies with greater regulatory predictability, which fosters continued investment in research and development. This has been illustrated by the significant number of approvals occurring during the COVID-19 pandemic, which is a testament to the Agency's commitment to the public health and the dedication of biopharmaceutical companies to drive medical advancements despite the ongoing challenges of COVID-19.

PDUFA VII will strengthen regulatory review fundamentals while enhancing accountability, transparency, and resource management at FDA. The overarching PDUFA VII efforts build on successes of the previous cycles and are aimed at modernizing the US regulatory and drug development paradigm and addressing new areas such as digital health technologies, cell and gene therapies, and manufacturing.

PDUFA VII also includes commitments that advance emerging COVID-19 lessons learned. FDA and the biopharmaceutical industry are utilizing novel approaches to clinical trials and facility inspections to support continued innovation and operations during the pandemic and to inform efficient regulatory decision-making to address COVID-19. The PDUFA VII provisions leverage lessons learned in adapting to and meeting the challenges presented by the COVID-19 pandemic, enhancing our future preparedness and ability to keep pace with scientific advancements.ⁱⁱⁱ

Through the targeted improvements outlined in the draft PDUFA VII commitment letter, the PDUFA VII agreement will have a lasting and meaningful impact on the biopharmaceutical industry's ability to develop innovative, safe, and effective medicines for patients in a timely manner. Specifically, PDUFA VII will:

- strengthen scientific dialogue and advance innovation;
- enhance patient-centric drug review and support safety monitoring;
- support the next wave of advanced biological therapies;
- modernize regulatory evidence generation and drug development tools;
- advance digital technologies and IT infrastructure;
- enhance innovation in manufacturing and product quality reviews; and
- build on PDUFA VI efforts to modernize FDA financial and staff resource management.

Specifically:

PDUFA VII Will Strengthen Scientific Dialogue and Advance Innovation

Effective interactions with FDA throughout development, from the pre-investigational new drug (IND) phase to the clinical development phase, can help minimize the risk of late-stage drug development failures, increase the probability that safety and efficacy data are available in a timely manner and mitigate issues that would delay patient access to approved treatments. PDUFA VII will help expand opportunities to incorporate FDA feedback throughout the drug development process, including through formalized Initial Targeted Engagement for Regulatory Advice on CDER/CBER Products (INTERACT) meetings for innovative products early in development. PDUFA VII will also provide for the creation of a new formal Type D meeting

with a shorter timeframe for focused discussion, including on innovative approaches, and enhanced processes and timelines for communicating and reviewing postmarketing requirements.

PDUFA VII proposed performance goals will also address regulation of combination products through new and enhanced procedures, timelines and guidance for human factor validation protocols and use-related risk analysis. In addition, PDUFA VII will support the development of treatments for rare diseases with the establishment of new pilot programs for supporting efficacy endpoint development and will establish a Split Real Time Application Review (STAR) to shorten the approval timeline for certain novel uses of approved therapies. Streamlined processes and prompt FDA feedback on sponsor questions and pressing development issues will help ensure regulatory efficiency and predictability for drug development programs involving innovative approaches.

PDUFA VII Will Enhance Patient-Centric Drug Review and Support Safety Monitoring

Through the Patient-Focused Drug Development (PFDD) Initiative established as part of PDUFA V^{iv} and continued in PDUFA VI,^v FDA has gained a better understanding of the disease, condition, and treatment elements that are of greatest importance to patients. PDUFA VI also provided significant resources to support the Agency's ability to review, track, and communicate important post-market safety information. This included an investment to expand the Sentinel System's capabilities and enhance the communication process with stakeholders on the use of Sentinel data.

PDUFA VII's proposed performance goals will build on initiatives from PDUFA V and VI and advance the incorporation of patient-centric data into drug development and regulatory reviews. Enabling further incorporation of the patient perspective, including through guidance on patient preference information, and expanded FDA staff training and outreach, will help enhance the patient-centric process by which the industry develops new medicines that address the needs of patients.

Implementation of the proposed PDUFA VII performance goals will also improve Risk Evaluation and Mitigation Strategies (REMS) assessments and advance Sentinel capabilities. PDUFA VII will establish new timelines for FDA review of methodological approaches and study protocols for REMS assessments. PDUFA VII will also advance the Sentinel analytical capabilities to support the use of Sentinel to address questions of product safety and address how real-world evidence (RWE) can be used for studying a drug's effectiveness.

Recognizing the importance of understanding and improving safety for all patients, PDUFA VII includes new Sentinel demonstration projects for assessing drug safety in pregnancy and the outcomes of pregnancies in women exposed to drugs and biological products. These activities will support implementation of a standardized process for determining necessity and type of pregnancy postmarketing studies,

PDUFA VII Will Support the Next Wave of Advanced Biological Therapies

A significant area of focus in modern drug development is the field of cell and gene therapies, which aim to treat, prevent, or cure disease by targeting the underlying cause through delivery of targeted cells or genetic material. Cell and gene therapy research holds tremendous promise in leading to the possible development of specialized treatments for patients with a variety of conditions, including genetic diseases, cancer, and infectious diseases.

Implementation of the proposed PDUFA VII performance goals will help ensure the efficient review of applications and timely patient access to innovative biological therapies regulated by FDA's Center for Biologics Evaluation and Research (CBER), including cell and gene therapies. FDA will provide further guidance to support the use of expedited programs for regenerative medicines, improve communication best practices, facilitate review of manufacturing information for products with accelerated clinical development, and advance PFDD activities. PDUFA VII also includes a public process to inform ways cell and gene therapy manufacturers can appropriately leverage a sponsor's internal prior knowledge and public knowledge across therapeutic areas to facilitate development and review of cell and gene therapies.

The proposed PDUFA VII performance goals will also help enable broader use of novel clinical trial designs and approaches for small patient populations and evaluate their application to more common diseases. CBER will be provided dedicated resources to facilitate necessary hiring and training reviewers for these transformative therapies.

PDUFA VII Will Modernize Regulatory Evidence Generation and Drug Development Tools

PDUFA VII will build on successful initiatives from previous PDUFA cycles and authorities in the 21st Century Cures Act to further modernize regulatory evidence generation and drug development tools, including advancing the appropriate use of real-world evidence (RWE) and real-world data (RWD) in regulatory decision-making. Delivering new medicines to patients through biomedical innovation requires advancing the development and application of the latest regulatory science approaches to drug development. New and powerful tools emphasize individual patient characteristics and include complex innovative clinical trial designs, the use of RWE, patient-reported outcomes, and advanced statistical methods. PDUFA VII initiatives will help advance regulatory evidence generation and the use of innovative clinical trial approaches and statistical models as well as increase transparency and promote stakeholder learning around acceptable uses of innovative approaches for regulatory decision-making. These initiatives include the establishment of a new pilot program to advance the use of RWE for regulatory decision-making, including for approval of new indications or to satisfy postmarketing study requirements, holding public workshops, and issuing guidance documents on the use of RWE.

PDUFA VII will also facilitate greater use of innovative clinical trial designs by advancing the use of complex adaptive and other novel clinical trial designs, including guidance on Bayesian approaches, and continuing the complex innovative trial design pilot put in place as part of the PDUFA VI commitments. PDUFA VII will also further advance consistency and predictability around the use of modeling and simulations, including model-informed drug development (MIDD) approaches, in regulatory decision-making.

PDUFA VII Will Advance Digital Health Technologies and Information Technology (IT) Infrastructure

PDUFA VII will help usher in the future of innovative biopharmaceutical R&D and regulatory review by advancing the use of digital health technologies (DHTs). DHTs – such as digital health products, artificial intelligence, and machine learning – present significant opportunities to support clinical trials and enable remote or decentralized clinical trials. Importantly, decentralized clinical trials have the potential to increase enrollment opportunities and provide access to more diverse patient populations.

PDUFA VII will establish a robust and efficient framework to facilitate the adoption of innovative digital health products, as well as promote coordination and utilization of DHTs in regulatory decision-making across FDA.

PDUFA VII initiatives will also help facilitate a modernized technology infrastructure to underpin and support the FDA’s regulatory review process. FDA’s data and IT capabilities will be enhanced during PDUFA VII, including, improved support for the review of DHT-generated data, and increased bioinformatics and computational biology capacity to enable review of complex biological data, such as Next Generation Sequencing. PDUFA VII will also help resource the cloud-based modernization of the Electronic Submissions Gateway (ESG) with an improved architecture that supports expanding data submission bandwidth and storage. FDA will also enhance accountability and transparency for the Agency’s IT modernization plans by establishing a strategy on data-driven regulatory initiatives that will build on FDA’s ongoing efforts as outlined in the Agency’s Technology Modernization Action Plan (TMAP) and Data Modernization Action Plan (DMAP).

PDUFA VII Will Enhance Manufacturing and Product Quality Reviews

For the first time in the history of PDUFA, manufacturing and product quality reviews will be addressed through provisions in PDUFA VII. Manufacturing and quality play a vital role in the drug development process and ensuring timely patient access to innovative medicines. In each reauthorization of PDUFA, FDA and industry have further defined the review process for marketing applications to help ensure that the Agency’s review remains on track and allows applicants visibility into FDA’s review for purposes of increasing first cycle approvals for those applications that are approved by FDA. PDUFA VII will help promote a more efficient review process, advance the use of innovative manufacturing technologies across product platforms and manufacturing sites, and establish a new pilot to facilitate Chemistry, Manufacturing and Controls (CMC) readiness for products with accelerated clinical development timelines. PDUFA VII also includes a commitment for FDA to issue guidance on the use of alternative tools to assess manufacturing facilities named in pending applications, including incorporation of best practices from the use of such tools during the COVID-19 pandemic.

PDUFA VII Will Build on PDUFA VI Efforts to Modernize FDA Financial and Resource Management

Transparency into and accountability for the use of user fee resources is a core pillar of the Program and of utmost importance to the biopharmaceutical industry. PDUFA VI included improvements to the financial structure of the PDUFA program^{vi} aimed to help ensure financial stability and appropriate staffing for the FDA to meet negotiated goals, with implementation and maturation of these reforms expected to continue into PDUFA VII. PDUFA VI also included improvements to the hiring process and set goals for the hiring of new staff that was needed to fulfill the human drug review program mission. PDUFA VII will build further on the foundational work started in PDUFA VI to help improve accountability and transparency and modernize financial and staff resource management. PDUFA VII includes hiring goals and improvements to recruitment, hiring, retention and training to help ensure that FDA has adequate staffing and can fulfill the commitments outlined in PDUFA VII.

Perspectives on the Success of the BsUFA Program

Biosimilars are playing an increasingly critical role in bringing new treatment options to patients and increasing competition. BsUFA has been essential to strengthening the FDA's ability to implement a regulatory review approach for biosimilar products that is consistent with the Agency's high standards, and the Program has resulted in 33 FDA-approved biosimilar products to date, including two interchangeable biosimilars.

The BsUFA III initiatives will build on the success of the Program and enhance FDA's biosimilar review process while ensuring stability and continued maturation of the Program. In helping provide FDA with the resources needed to enhance the development and review of biosimilars, BsUFA III will, in turn, help increase competition in the marketplace to the benefit of patients. Specifically, BsUFA III will:

- enable timely sponsor interactions with FDA for biosimilars development and review;
- establish timelines for review of certain application supplements, including those seeking to update safety labeling to reflect changes to the reference product labeling;
- advance development of interchangeable biosimilar products and pilot a regulatory science program;
- enhance manufacturing inspection-related communications and modernize facility assessment approaches;
- modernize FDA's IT infrastructure and support adoption of cloud-based technologies; and
- build on BsUFA II efforts to modernize FDA financial and staff resource management.

Specifically,

BsUFA III Will Enable Timely Sponsor Interactions with FDA for Biosimilars Development and Review

BsUFA III will enable timely interactions between sponsors and FDA during biosimilar development and review. Specifically, BsUFA III includes modifications to existing meeting types such as modification of the current Biosimilar Initial Advisory (BIA) meeting to provide flexibility for discussion of biosimilarity prior to the availability of preliminary comparative analytical data and establishment of a new meeting type for rapid, targeted feedback to assist sponsors during biosimilar product development.

BsUFA III Will Establish Timelines for Review of Certain Application Supplements, Including Those Seeking to Update Safety Labeling to Reflect Changes to the Reference Product Labeling

BsUFA III will enhance consistency and predictability of the biosimilars review process by establishing specific timelines for review of certain application supplements, including those seeking to update safety labeling to reflect changes to the reference product labeling.

BsUFA III Will Advance Development of Interchangeable Biosimilar Products and Pilot a Regulatory Science Program

BsUFA III will provide information and guidance to sponsors for development of biosimilar and interchangeable biosimilar products. FDA will issue guidance and hold a corresponding public workshop on topics foundational for the development of interchangeable biosimilar products. FDA will also pilot a regulatory science program with demonstration projects and deliverables focused on advancing the development of interchangeable biosimilar products and improving the efficiency of biosimilar product development. Informed by the pilot program, FDA will develop and publish a comprehensive strategy outlining specific actions the Agency will take to facilitate the development of biosimilar and interchangeable biosimilar products.

BsUFA III Will Enhance Manufacturing Inspection-related Communications and Modernize Facility Assessment Approaches

As with PDUFA VII, the BsUFA III agreement includes dedicated initiatives to address manufacturing for the first time in the history of the Program. In response to the significant challenges presented by the COVID-19 pandemic to foreign and domestic inspections, FDA employed the use of alternative tools and a risk-based approach to ensure the safety and continuity of the global biopharmaceutical supply chain. BsUFA III will advance use of alternative inspection tools (e.g., requesting records and other information directly from facilities and other inspected entities, utilizing new or existing technology platforms to assess manufacturing facilities as appropriate) to apply COVID-19 lessons learned beyond the current public health emergency. FDA will develop guidance on the use of alternative tools to assess manufacturing facilities named in pending applications, including incorporation of best practices

from the use of such tools during the COVID-19 pandemic. In addition, BsUFA III will promote timely FDA communication with sponsors regarding manufacturing facility inspections.

BsUFA III Will Modernize FDA's IT Infrastructure and Support Adoption of Cloud-based Technologies

As with the PDUFA VII agreement, BsUFA III will also provide dedicated resources and includes corresponding initiatives related to enhancing the capabilities of FDA's IT and data infrastructure to support the regulatory review of drugs. BsUFA III will help support a modernized, cloud-based ESG and also help with the establishment of a strategy on data-driven regulatory initiatives that will leverage the Agency's current initiatives as detailed in the TMAP and DMAP.

BsUFA III Will Build on BsUFA II Efforts to Modernize FDA Financial and Staff Resource Management

BsUFA II included improvements to the financial structure of the BsUFA program^{vii} aimed to help ensure financial stability and appropriate staffing for the FDA to meet negotiated goals, with implementation and maturation of these reforms expected to continue into BsUFA III. Implementation of the proposed BsUFA III performance goals will build on the foundational work started in BsUFA II to modernize financial and staff resource management, accountability, and transparency, including clear hiring goals and progress reporting.

Conclusion

America's biopharmaceutical research and development ecosystem is the best in the world. However, due to the ongoing COVID-19 pandemic and increased global competition, it is imperative that FDA is equipped to help us deliver new treatments and cures to meet patients' unmet medical needs. PDUFA VII and BsUFA III will help ensure that patients have timely access to lifesaving medicines, while maintaining the United States' global leadership in biopharmaceutical innovation.

PhRMA and its member companies are committed to working closely with FDA and all stakeholders to ensure the continued success of the PDUFA and BsUFA programs in bringing safe and effective medicines to patients. PhRMA therefore urges Congress to reauthorize PDUFA and BsUFA in a timely manner to ensure the new enhancements are implemented as planned and protect against any disruptions to these critical programs.

PhRMA applauds your continued commitment to ensuring the long-term stability of the FDA's human drug and biosimilar review programs and to continuing to strengthen the Agency's capabilities in areas critical to keeping pace with the latest scientific advances in drug development and regulation. We look forward to continuing to work with the Committee,

Members of Congress, and other stakeholders on these important issues. Thank you for the opportunity to provide this testimony. I would be happy to address any questions.

ⁱ PhRMA, “PhRMA 2021 Annual Membership Survey,” (2021), https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/M-O/PhRMA_membership-survey_2021.pdf

ⁱⁱ See U.S. Food and Drug Administration [hereinafter “FDA”], Center for Drug Evaluation and Research, “Advancing Health Through Innovation: New Drug Therapy Approvals 2021,” (January 2022), at 21, <https://www.fda.gov/media/155227/download>.

ⁱⁱⁱ See FDA, “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027,” [hereinafter “PDUFA VII Commitment Letter”] at 28, 49-50, <https://www.fda.gov/media/151712/download>.

^{iv} See FDA “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017,” at 22, 24-25, <https://www.fda.gov/media/81306/download>.

^v See FDA, “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022,” [hereinafter “PDUFA VI Commitment Letter”] at 27-30, <https://www.fda.gov/media/99140/download>.

^{vi} PDUFA VI Commitment Letter at 37-41.

^{vii} See FDA, “BsUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022,” at 27-32, <https://www.fda.gov/media/100573/download>.

Ms. ESHOO. Thank you very much, Doctor.

Now the Chair recognizes Dr. Esham.

You are recognized for 5 minutes , and thank you again for being with us today to testify on these important programs.

STATEMENT OF CARTIER ESHAM, Ph.D.

Dr. ESHAM. Thank you.

Good afternoon, Chairwoman Eshoo, Ranking Member Guthrie, and members of the committee.

My name is Cartier Esham, and I am the Chief Scientific Officer at the Biotechnology Innovation Organization, or BIO.

BIO appreciates the opportunity to speak with you today about the benefits of and vital need for the timely reauthorization of PDUFA VII and BsUFA III.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, and related organizations across the United States and more than 30 other nations.

While our membership includes most of the large international biopharmaceutical companies, the majority of our members are small pre-revenue companies working on cutting edge biomedical innovations.

Since 1992, the user fee agreements have collectively worked to ensure effective and timely reviews, improve safety management, enable the agency to keep pace with medical and scientific advancements, and continue to improve processes that allow for early issue identification and resolution where possible.

Those commitments continue to build on those successes with a focus on strengthening review fundamentals and ensuring the agency has the necessary resources and capabilities to meet current and projected needs to advance the development and availability of next generation medicines and biosimilars.

Today we will highlight a few of those provisions that serve to meet those goals, starting with the PDUFA commitment.

First, there are numerous commitments in PDUFA that will advance the utilization of patient-centric drug development and review processes. These include but are not limited to continued support for the utilization and review of patient perspective data and innovative clinical trial designs; expanding the ability to utilize real world evidence; advancing knowledge about how to develop acceptable endpoints for rare disease drug development; and strengthening the FDA's safety monitoring capabilities.

Additionally, PDUFA VII will provide much needed resources to ensure the FDA is able to take advantage of the digital age by improving the agency's analytic capabilities and supporting the use of digital technologies which have the potential to reduce patient burdens and more effectively capture information about clinical outcomes.

Second, it is critically important that CBER has the resources necessary to meet the demands of a vastly growing and exciting pipeline of cell and gene therapies. A 2020 analysis by BIO found that there were 231 gene therapy programs under development compared to 93 in 2015, a trend that is expected to grow in the coming years.

To ensure that new and innovative cell and gene therapy products can be effectively developed, reviewed, and available to patients in a timely manner, the commitment letter provides CBER with resources not just to increase personnel to meet growing workload, but also provides support for training needs and the ability to modernize data analytic capabilities.

The totality of the commitment to PDUFA will ensure the center's best position to keep pace with scientific advancements and more effectively community learnings and expectations to the entire research and development community.

Third, the ability to engage in a timely and effective scientific dialogue is fundamental to ensuring early issue identification and resolution, as well as creating clear pathways for the utilization of modern approaches to drug development.

The PDUFA agreement creates a new meeting opportunity that will allow FDA and sponsors to have focused conversations about unique challenges or innovative approaches.

There is an expansion of the ability to have early stage planning discussions prior to the submission of an IND to better enable alignment of expectations and minimize delays to clinics for medicines that have complex issues or lack clearly understood precedence.

And lastly, the PDUFA agreement will serve to improve review processes through more timely discussions and processes relating to post market commitment, CMC and manufacturing issues, and there is the ability and there is an expansion of tools and approaches the FDA can utilize to better manage inspection workloads.

Like the PDUFA agreement, the BsUFA agreement also works to ensure timely and productive scientific dialogue and advance the regulatory science in key areas.

Both agreements share a common goal, ensuring effective, efficient, and patient-centric drug development and review processes for the next generation of medicines. They both work to ensure the FDA has the ability to recruit and retain world class personnel and effectively manage resources.

BIO urges Congress to act swiftly and support timely enactment of these vital reauthorizations so that the FDA is best able to meet its mission of protecting and promoting the public health and that there will be clear pathways for approved availability of medicines that will improve the lives of patients and their families.

And before I close, I would also like to say that BIO is committed to enhancing and approving clinical trial diversity as part of our BIO's quality agenda.

We look forward to working with all of you on proposals that will help build a sustainable, more inclusive clinical development ecosystem.

Thank you.

[The prepared statement of Dr. Esham follows:]

**Testimony of Cartier Esham, Ph.D., Chief Scientific Officer
Biotechnology Innovation Organization**

**House Energy and Commerce Committee Hearing:
*FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics***

February 3rd, 2022

Chairman Pallone, Ranking Member McMorris Rodgers, Chairwoman Eshoo, and Chairman Guthrie, on behalf of BIO we appreciate the opportunity to speak with you today about the seventh reauthorization of the Prescription Drug User Fee Act (PDUFA VII). At the outset of the negotiation process there was strong alignment about which topics needed to be addressed in the PDUFA VII Commitment letter and the discussions during the process benefitted from learnings we were gathering during the COVID-19 pandemic. BIO strongly urges timely reauthorization of PDUFA VII and BsUFA III to ensure the FDA is best able to continue to meet its mission to protect and promote public health. I am Dr. Cartier Esham, Chief Scientific Officer at BIO. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organization across United States in more than 30 other nations. While our membership includes most of the large, international biopharmaceutical companies, most of our members are small biotechnology companies working on cutting-edge biomedical innovations. These companies are pre-revenue and take enormous risks every day to develop the next generation of biomedical breakthroughs for the millions of patients suffering from diseases for which there are no effective cures or treatments today. BIO is proud of their innovative spirit and dedication to improving the lives of patients and their families.

The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and authorizes FDA to collect fees from companies that produce certain human drug and biological products. PDUFA is reauthorized by Congress every 5 years and serves to provide the FDA with resources through fees paid by biopharmaceutical companies that are additional to those provided by Congress through appropriations. Congressional support and the PDUFA program together have made FDA the strongest and most advanced regulatory agency in the world. Since initial enactment of PDUFA, user fees have played an important role in ensuring effective and efficient processes are aligned with the continual advancement of scientific and medical innovation. The result is more innovative treatments and therapies are first approved in the United States providing our citizens with faster access to innovative medicines than anywhere

else in the world. Additionally, the PDUFA program serves to ensure the FDA has the resources, capabilities, and processes in place to chart a well-understood pathway from discovery to availability of cutting-edge medicines. This is important not only to regulators, patients, and the biopharmaceutical industry, but also to the entrepreneurial community that contributes significant investments in high-risk early-stage innovative medicines. Today, it can take anywhere from 10 to 15 years at an average cost approximately a \$1billion or more to advance a drug or biological product from a good idea to an approved product that benefits patients.^{1,2} A well-run and understood pathway to approval is critical to maintaining U.S. leadership in investment, development, and availability of next-generation medicines.

Overall Goals for PDUFA VII

Each user fee Commitment Letter has continued to build upon the efforts of previous agreements. The enacted PDUFAs have collectively worked to ensure effective and timely reviews, improve safety management, enable the Agency to keep pace with medical and scientific advancements, and allow for earlier issue identification and resolution where possible. Fundamentally, PDUFA VII is designed to build upon existing processes to strengthen review fundamentals, enhance accountability and transparency, ensure stable growth of the program, and initiate or advance critical medical and scientific advancements. The following testimony will describe the content and benefit of critical provisions addressing each of the following seven primary themes included in the PDUFA VII Commitment Letter:

- Strengthen scientific dialogue and advance innovation
- Support the next wave of advanced biological therapeutics
- Enhance patient-centric drug development, review and protections
- Modernize regulatory evidence generation and drug development tools
- Enhance innovation in manufacturing and product quality reviews
- Advance digital technologies and information technology (IT) infrastructure

¹ Olivier J. Wouters, PhD; Martin McKee, MD, DSc; Jeroen Luyten, PhD. Estimated Research and Development Investment Needed to Bring a New Medicine to Market JAMA. 2020, 323(9).

² Joseph A. DiMasi; Henry G. Grabowskibi; Ronald W. Hansen. Innovation in the pharmaceutical industry: New estimates of R&D costs. 2016. Journal of Health Economics. 2016, Vol. 47.

- Enhance FDA hiring, retention, and financial management

Strengthen scientific dialogue and advance innovation

One of the most important goals of PDUFA VII critical to advancing innovation is to continue to enhance and strengthen scientific dialogue between sponsors of applications and the FDA. To that end, FDA will provide timelines and expand the Initial Targeted Engagement for Regulatory Advice (INTERACT) pre-Investigational New Drug Applications (INDs) meetings to include clinical development programs intended to be reviewed by CDER as well as CBER that have a novel challenges where early engagement with the FDA is critical to avoiding delays in advancing entry into to the clinic. These have been previously limited to products under review by CBER. FDA will also establish a new Type D meeting that enables the FDA and sponsors to engage in focused conversations about innovative approaches or unique challenges that will allow for earlier resolution of issues and understanding of what is required to better ensure stronger applications for review. The Commitment Letter also provides for a process where sponsors can submit clarifying questions to the FDA following a meeting to better ensure aligned understanding of expectations and requirements. We collectively recognized that best practices for productive meetings is a shared responsibility between biopharmaceutical companies and the FDA. PDUFA VII calls for the training of FDA staff and a public workshop to discuss and share best meeting practices that will inform the publication of updated guidance documents describing how to conduct and prepare for meetings that are productive, informative, and serve to efficiently advance clinical development programs and review processes more consistently.

There are at least 7,000 known rare diseases collectively impacting over 25 million Americans and new rare diseases are identified each year. Providing treatments and cures for these patients is complicated by the fact that the development and review of these medicines is often conducted without well-established regulatory precedents because there are limited or no available treatments for these diseases. Clinical trial populations for rare diseases are small and our understanding of the natural history of the disease may be limited which create additional challenges for those developing innovative treatments and cures and for those that are regulating their approvals. Key among these challenges is reaching agreement with regulators about determining the appropriate efficacy endpoints to support approval of innovative medicines for rare diseases. Additionally, the current mechanisms for companies of rare disease drug development programs to collaborate with FDA has not consistently provided

avenues for much needed discussions about these unique issues and can cause delays in advancing the development and availability of medicines to these patients which often have limited or no options. The Rare Disease Endpoint Advancement pilot program in PDUFA VII will provide avenues for focused engagement opportunities for a designated number of eligible applications that have a proposed novel efficacy endpoint. This pilot program also includes commitments such as public workshops and guidance documents that will serve to share learnings and advance more efficient development and review approaches and processes for all rare disease medicines to provide much needed cures or improved quality of life for these patients and their families.

The Commitment Letter will establish a Split Real Time Application Review (STAR) pilot program for certain supplemental New Drug Applications (NDAs) that are intended to treat a serious condition with an unmet need. The pilot is built on the concepts that have proven successful for the Real Time Oncology Review (RTOR) program. The STAR pilot is designed to improve workload management by allowing sponsors of applications to submit their applications in 2 parts allowing for earlier review of key components such as proposed labeling, clinical protocols and topline efficacy and safety results prior to the final application submission. The objective of this pilot is to enable more timely reviews and availability of these medicines similar to the observed RTOT program results. This pilot will also enable the FDA to assess potential benefits or challenges of expanding this program in the future which will be shared via a public workshop that includes an opportunity for feedback prior to the next PDUFA reauthorization.

Biopharmaceutical companies and the FDA recognize the importance of post-marketing requirements (PMRs) to ensure timely availability of information on the safety and efficacy of certain therapies to patients when further post-approval studies are warranted. PDUFA VII aligns processes to ensure necessary discussions are occurring in a manner that allow for more effective assessments of whether a PMR is needed and provide timelines that enable more thoughtful development of PMR studies. PDUFA VII will also establish stronger processes for the continued evaluation of PMRs post-approval to ensure requirements are being met and/or remain scientifically valid.

Support the next wave of advanced biological therapies

Advancing the new wave of biological therapies is a top priority for BIO member companies. A 2020 analysis by BIO found that there were 231 gene therapy programs under development

compared to 93 programs in 2015, a trend that is expected to grow in the coming years. To ensure that new and innovative cell and gene therapy products are developed and available to patients in a timely manner, the Commitment Letter will provide FDA the resources and capacity needed to address the growing workload of the Cell and Gene Therapy Program. This will enable FDA to maintain the level of highly-trained and experienced Cell and Gene Therapy staff needed to address the growing number CBER workload projected over the next 5 years, as well as keep pace with scientific and technological advancements.

Specifically, PDUFA VII establishes commitments, engagements and publication of information or guidance to advance shared understandings about the inclusion of patient perspective data in the development of cell and gene therapies, the utilization of novel endpoints and innovative clinical trial designs for small patient populations. CBER will also issue Question and Answer guidance addressing frequently asked questions and commonly faced issues to better inform clinical development programs about the current thinking of FDA. Additionally, CBER will hold public meetings and issue guidance of utilization for capturing post approval safety and efficacy data for cell and gene therapy products and update guidance on expedited pathways for regenerative medicines including information to better align expectations for Chemistry, Manufacturing and Controls (CMC) readiness which has been a barrier to timely access to breakthrough cell and gene therapies. And lastly, PDUFA VII includes commitments by CBER to work with key stakeholders to foster the development and accessibility of non-proprietary knowledge (e.g. standards), manufacturing advancements, and manufacturing components that will serve to better facilitate the development, review, production and availability of these innovative therapies domestically and around the world.

Enhance patient-centric drug development, review and protections

One of the most important goals of PDUFA VII are the commitments to continue to advance the systematic integration of patient perspective data into drug development programs and review processes. This work began in earnest under PDUFA V with the establishment of the Voice of the Patient Program that supported public meetings where patients provided insights about their conditions and how they evaluated benefits, risks and needs. PDUFA VI advanced this work by holding a series of public meetings and the publication of guidance that provided information about how to determine the most important impacts to patients, how measure disease impact and how to incorporate Clinical Outcome Assessments (COAs) into clinical development programs and review processes.

During PDUFA VII, the FDA will continue this critical work by continuing to strengthen capacity and knowledge through the expansion of training opportunities for FDA staff and ability to better engage external methodological experts. The FDA will seek public input on methodologies and approaches for the submission of high-quality patient perspective data designed to inform benefit-risk assessments and inclusion of information in the label. PDUFA VII will provide supplementary support to the FDA to support the continued development of a publicly available virtual catalog of Standard Core Sets of COAs and related endpoints that will help make possible the broader utilization of patient perspective data in clinical development programs. The FDA will also seek public input on which diseases areas have the greatest need for the Standard COA development. Additionally, the FDA will work to increase shared understandings about how patient preference studies can inform meaningful benefit-risk assessments in therapeutic areas.

To enhance the FDA drug safety system, PDUFA VII provides resources and processes that will enable the adoption of new scientific approaches designed to improve the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events. Steps will be taken to modernize and improve Risk Evaluation and Mitigation Strategies (REMS) approaches and processes. Specifically, PDUFA VII will update guidance to better ensure appropriate and sufficient safety evidence are collected and provide information about what type of data are needed to eliminate the need for a REM. Further, goals will be put in place to allow for consistent and timely feedback on submitted REMS methodologies and protocols. Resources will also be provided to continue to expand and optimize the FDA's electronic safety data base (the Sentinel program) including supporting the integration of Sentinel and BEST (Biologics Effectiveness and Safety) systems. Additionally, the FDA will build on current communications and advance knowledge about how Sentinel data can be used for regulatory purposes (*e.g.* PMRs, PMCs and labeling) and to advance understandings about how real-world evidence (RWE) may be used for evaluating the effectiveness of medicines. Collectively, these improvements and advancements in the FDA the drug safety system will improve patient protections and utilization of this vast data resource to gain deeper and continual understandings about the benefit and risks of medicines.

Modernize regulatory evidence generation and drug development tools

Advancing innovative, patient centric drug development tools, and modernizing the regulatory evidence generation paradigm is a top priority for BIO member companies. Advancements in science and technology offer real opportunities to reduce patient burden, improve ability to recruit and conduct effective clinical trials and provide more informative analyses of benefit and risk pre and post approval. PDUFA VII will continue to build on several key initiatives that were launched under PDUFA VI. Under this Commitment Letter the FDA will advance the use of real-world evidence (RWE) to support approval of labeling claims, approval of new indications and to satisfy post approval study requirements. There will be an Advance RWE pilot program established that provides increased interactions for a select number of applications that collectively will provide shared learnings with the public and inform the publication of guidance increasing broad knowledge about how and when RWE can be utilized. PDUFA VII will also continue both the Complex Innovative Trial Design and Model-Informed Drug Development (MIDD) pilot programs which similarly provide increased engagement and publication of learnings to enable the utilization of these tools and approaches more broadly. Complex innovative trials such as adaptive and Bayesian approaches can be more efficient, improve patient outcomes and produce high-quality information faster. Additionally, the Agreement will work to enhance the drug development tools qualification pathway for biomarkers by retaining and enhancing staff capacity and piloting of processes to engage external experts to support the review of biomarker qualification submissions. High quality biomarkers can accelerate and enable drug development in areas of unmet need, improve clinical trial feasibility and efficiency thus continued improvement of the qualification pathway is beneficial to regulators, the research and development community, and patient communities.

Enhance innovation in manufacturing and product quality reviews

One of the critical needs for PDUFA VII was to advance innovation in manufacturing and inspection review processes and improve the ability to get medicines to patients in a timely manner. A rate-limiting step for the past several years have been discussions and resolution of chemical manufacturing and control (CMC) issues, especially for innovative biologic therapies and treatments. FDA will improve the timeliness and effectiveness of CMC communications through training and updating CDER and CBER guidance designed to better enable more consistent review of high-quality information requests from sponsors. The FDA will also engage a third party to assess, seek public comment and provide recommendations about how these processes can be optimized.

To address the outsized hindrance of timely availability of innovative treatments for serious and life-threatening diseases undergoing expedited reviews due to CMC issues, the FDA will publish new internal documents to better align CMC communications and processes to better meet the desired timelines for approval decisions. The FDA will also establish a CMC Development and Readiness Pilot (CDRP) at both CDER and CBER. The CDRP pilot is designed to improve CMC readiness for IND applications through increased engagements to improve alignment on what is needed and when to meet critical CMC milestones. Learnings from this pilot will be made available to the public via a public workshop and the publication of a strategy document describing the Agency's plans to revise processes and information about submission strategies to accelerate CMC development.

Over the past several years there have been significant scientific advancements about how to manufacture high-quality complex medicines effectively and efficiently. PDUFA VII will work to identify and remove current barriers to their utilization and adoption. The FDA will conduct a workshop where best practices, case studies and regulatory strategies will be shared and discussed, including how to assess innovative technologies across platform products and sites. These discussions will inform the publication of a draft strategy document about the facilitation of the utilization of innovative manufacturing technologies and inform the publication of guidance, internal process documents and other recommended actions.

During the COVID-19 pandemic, regulators, biopharmaceutical companies and other key stakeholders from around the world held discussions about how best to ensure the continued availability of medicines and meet the needs of providing COVID vaccines and treatments to all in need. Among the results of those discussions were the increased utilization, when appropriate, of alternative tools such as use of information shared by trusted foreign regulatory partners and record requests for assessing manufacturing facilities. PDUFA VII will continue the advancement of those lessons learned by issuing draft guidance about when and how these types of alternative approaches may be utilized beyond the pandemic.

Advance digital technologies and information technology (IT) infrastructure

It is of vital importance that support be provided to the FDA to increase its capacity and ability to meet the demands of the data and digital age. Increasing utilization of cloud technologies is necessary for the FDA to meet the growing needs, demands and advantages of modern-day

development and review of innovative medicines. The clinical development programs and applications of today have large and/or complex data sets that require high-quality repository and analytical capabilities. PDUFA VII activities and resources, collectively, will serve to enable the FDA to make the necessary changes to meet these needs. These advancements will serve to improve the quality of applications submitted to the FDA and improve our ability to better understand the benefits and risks of medicines to all patients before and after they are approved.

First, the FDA will continue to meaningfully advance their Data and Technology Modernization Strategy. This Commitment includes timelines for articulation and communication of goals and communication about how these strategies are developed and implemented and serve to improve both FDA enterprise needs and to advance key PDUFA objectives. Specific needs such as improving the ability to electronically submit applications via increasing band-width of the electronic gateway systems (EGS) and completing transition to a cloud-based system are expected to be completed. The FDA also committed to regular engagement with the biopharmaceutical industry to provide progress updates, share learnings, and discuss challenges in meeting PDUFA VII goals and advancing objectives outlined in the Data and Technology Modernization Strategy.

Second, the FDA will launch a series of demonstration projects to improve the ability to review data captured via digital technology tools. We have seen and expect to see continued growth in the utilization digital technologies as they offer the ability to reduce burdens on patients in clinical trials, better assess clinical outcomes for all patients, and more efficiently collect high-quality data and evidence to support approvals and inform life-cycle management of medicines. Under PDUFA VII, the FDA will engage with external parties to develop core capabilities to ensure high-quality data collection, sharing and review of data, including the adoption of cloud-based technologies, to enable productive regulatory-applicant interactions. The FDA will also launch a series of demonstration projects focused on: enhancing capabilities to effectively receive and review digital health technology derived data; demonstrate utilization of cloud-based technologies to support application-regulator interactions and needs; and, develop technical capabilities needed to enable utilization and review of applications with data collected via digital technology tools. Findings and planned next steps from these demonstration projects will be shared with biopharmaceutical companies and made available to the public on FDA's website.

Third, critical IT modernization and capacity needs for the review of Biologic License Agreements will be provided to CBER to meet the demands of current and future applications that are projected to increase significantly over the next five years. In coordination with the Data Technology Modernization Strategy described above, CBER will develop a specific multi-year modernization roadmap to chart specific steps necessary for CBER to meet current and projected needs necessary to continue to successfully carryout its mission. Specially the roadmap is charged with designing a plan that will enable more efficient and effective exchange of information, data analyses, dissemination of safety information and support consistent review processes. Like the Data Technology Modernization Strategy commitments, communications, progress and next steps will be shared with the biopharmaceutical industry and the public. And lastly, resources will be provided to improve the FDA's bioinformatics capabilities (e.g. Next Generation Sequencing). The use of bioinformatics is expected to grow and provides tremendous insights about the quality, safety, and efficacy of biologics. These additional resources will enable the FDA to conduct in-depth independent analysis of submitted data BLAs and support the publication of guidance documents to ensure up-to-date review criteria and processes for next-generation biologic treatments and therapies.

Enhance FDA hiring, retention, and financial management

PDUFA VII continues to build upon the resource management and fiscal accountability provisions included in PDUFA VI. For example, the time reporting system initiated under the previous Agreement will be optimized to allow for time and associated costs to be reported and examined on a more continual basis. Additionally, to strengthen fiscal and staff resource management, accountability, and transparency, PDUFA VII will continue to mature the resource capacity planning system that includes a publication of an updated implementation plan describing how resource capacity planning and time reporting will be improved and implemented over the coming 5-year PDUFA cycle. A third-party assessment of the capacity planning system will be conducted and inform the 5-year fiscal planning activities. Recommendations and findings of this assessment will be included in the annual financial reports. Additionally, FDA will maintain a stronger operating reserve to ensure they are better able to mitigate against disruptions to funding resources and continue to carry out mission critical activities.

Ensuring the FDA is able to recruit and retain world-class personnel is the bedrock for maintaining U.S. regulatory leadership around the world. PDUFA VII continues to provide

resources and tools to better enable the FDA to attract and retain leading medical and scientific professionals. Specifically, PDUFA VII provides the FDA with resources to conduct a third-party assessment of hiring and retention to identify challenges and provide recommendations for the Agency. These recommendations will be made available to the public where the FDA will also share its plans to address issues raised.

BsUFA Highlights

The Biosimilar User Fee Agreement (BsUFA) contains several commitments that have the same goals and objectives as those included in PDUFA VII including, maintaining and improving performance goals for the effective and timely review of biosimilars, improving scientific dialogue, best meeting practices, modernizing IT capabilities, advance utilization of RWE to assess safety and support regulatory decision making, and strengthening the ability to recruit and retain world-class personnel. Below I will highlight a few of the key beneficial provisions included in the BsUFA III Commitment Letter.

Improving Scientific Dialogue

Ensuring timely scientific dialogue throughout the review process is a top priority for BIO member companies. BsUFA will improve the ability to engage in timely and focused discussions through the creation of new and improved meeting opportunities. Specifically, the FDA will now provide a new meeting structure that enables the FDA and sponsors of applications to engage in focused conversations on a narrow set of issues. Under the new structure a sponsor can request a dedicated meeting to discuss feedback on things like revised study designs or discuss CMC post-approval commitment. They can also request a dedicated meeting to discuss specific issues such proposed study designs or review of summary data.

BsUFA III also reforms the biosimilar initial advisory (BIA)³ advisory meeting process designed to better manage FDA workload and ensure productive discussions about whether licensure of a biosimilar is feasible, and, if so, plans and expectations for the development of that biosimilar.

³ A BIA meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the PHS Act may be feasible for a particular product, and if so, general advice on the expected content of the development program.

Improving Review Processes of Biosimilar Supplemental Applications

The BsUFA III agreement will bring more predictability and efficiency to the review of supplements. Specifically, there will be timelines and goals established for 6 different types of supplement categories (updating of label with new safety information (3 mos.), additional indications where new data is not required (4 mos.); removal of an approved indication (4 mos.) additional indications where new data is required (6 mos); additional indications that includes efficacy data (6 mos. for resubmission, 10 mos. for original application); and, applications seeking an initial determination of interchangeability (6 mos. for resubmission, 10 mos. for original application). These commitments will increase efficiency, consistency, and predictability of biosimilar supplemental applications and provide patients with timelier access to these medicines.

Advancing the Development and Review of Interchangeable Biosimilars

BsUFA III will work to continue support more efficient and understood processes for the approval of interchangeable biosimilars. The FDA will hold a scientific workshop to discuss and shared learnings and remaining challenges to the development of interchangeable biosimilars that will serve to help the FDA determine what additional steps need be taken to support the development and availability of these medicines (e.g. additional guidance or research). Following the workshop, the FDA will publish a strategy document describing the specific actions the FDA will implement to facilitate development of interchangeable biosimilars.

To advance regulatory science in this field, the FDA will pilot a regulatory science program that is designed to advance the development of interchangeable products and improve the efficiency of their development. Specifically, this pilot program will work to improve knowledge about how data (including RWE) can be utilized to meet safety standards for determining interchangeability and what methodologies can be utilized to assess the potential impact of differences between proposed interchangeable biosimilars and their reference products. The findings and shared learnings from this pilot program will greatly advance the development, review and availability of interchangeable biosimilar medicines.

Interchangeable Biosimilar Labeling and Manufacturing Guidance

Under BsUFA III the FDA will publish guidance to that will serve to improve communication of important biosimilar labeling information to patients and their caregivers and better facilitate resolution of manufacturing issues. Specifically, the FDA will publish a guidance on labeling for

interchangeable biosimilars, a guidance on promotional labeling and advertising considerations for interchangeable biosimilar products, and a guidance on what information is needed to support post-approval manufacturing changes to approved biosimilar and interchangeable biosimilar products. Collectively, these will serve to provide a greater understanding of what is required for efficient review and approval of changes to labels and manufacturing processes.

Closing Comments

BIO strongly supports the PDUFA VII and BsUFA III Commitment Letters. The resources provided will serve to maintain FDA's global leadership and enable the Agency to keep pace with the medical and scientific advances of today and tomorrow. BIO urges Congress to act swiftly and support timely enactment of these vital critical reauthorizations so that the FDA is able efficiently and effectively protect the public and provide timely access to medicines to medicines that improve the lives of patients and their families.

Ms. ESHOO. Thank you.

It is now my pleasure to recognize Ms. Reed. You have 5 minutes for your opening statement.

STATEMENT OF JULIANA M. REED

Ms. REED. Thank you, Chairwoman Eshoo, and thank you, Ranking Member Guthrie and members of the committee.

My name is Juliana Reed, and I am the Executive Director of the Biosimilars Forum. On behalf of the Forum members, I would like to thank you for inviting me to participate in the hearing today.

This is an especially significant hearing for me not only to represent the biosimilars industry in the United States, but like you, Chairwoman Eshoo, I have been committed to advancing patient access to lower cost biosimilar medicines since we worked on this together to pass the BPCIA years ago.

It is exciting to think we are on our third user fees, but as we know, even more needs to be done to advance biosimilars.

The Forum is a nonprofit trade association representing the companies with the most significant U.S. biosimilars development portfolios. Our members include Biogen, Boehringer, Engelheim, Coherus Biosciences, Organon, Pfizer, Samsung Bioepis, Sando, Teva, and Viatris.

My remarks today represent the views of our members, all of whom manufacture or market biosimilar products in the U.S., as well as other parts of the world.

Biosimilars have the potential to provide very significant healthcare savings in the U.S. Without robust competition, innovator biologics will continue to represent approximately 40 percent of the total prescription drug spending, while they represent only four percent of the medicines prescribed to patients.

Biosimilars provide competition to allow Americans access to lower cost medicines, and their timely licensure launch is vital to ensuring patient access to lower cost biologic medicines.

The Biosimilars Forum is supportive of the negotiated BsUFA III agreement, and we believe it represents important progress in facilitating timely access to safe and effective biosimilar medicines for patients.

We are pleased the commitment letter codifies review timelines for labeling supplements, provides meeting management enhancements, and promotes best practices of communication between FDA and sponsors.

The Forum is particularly pleased the BsUFA III program will include a regulatory science program that can help bring more biosimilars to market faster.

Since the BPCIA was enacted over a decade ago, there have been many advances in the science of developing biologic drugs. The regulatory sciences program will provide FDA and industry the ability to incorporate the latest scientific innovations into biosimilar development and regulations.

Although we are very satisfied with the progress represented in BsUFA III, we want to stress that the pandemic has impacted biosimilars and patient access disproportionately hard for almost two years. COVID-19 has stalled on-site inspections for biosimilars, delaying their approvals.

While biosimilar inspections have been delayed for the past two years, on-time actions for the GDUFA and PDUFA programs have averaged over 90 percent, and the BsUFA program plunged to 75 percent during the fourth quarter of 2020 and further dropped to 67 percent in 2021 where it remains today.

Per the agency's May 2021 roadmap for FDA inspection oversight, biosimilars' actions are not considered mission critical and thus they are not prioritized.

This has the ultimate outcome of slowing timely approval for biosimilars. We would like to ask the FDA for clarity to sponsors and the public as to the estimated timelines the FDA believes it will take to address this backlog.

For the BsUFA III commitment letter to be a success, the inspection backlog for biosimilars must be addressed, and remote inspections be implemented consistently across all programs. Biosimilars cannot remain a low priority for the agency.

The Forum is encouraged by the FDA's commitment to hire and retain sufficient numbers and types of technical experts to efficiently conduct review and applauds the agency's efforts to improve its use of data and technology.

We will work with the FDA to determine how we can allocate reviewers specifically for BsUFA goals. Industry understands FDA staff works on numerous types of applications. A small cadre of focused biosimilar staff could help expedite the assessment in the inspection process for biosimilars.

As we head into BsUFA III, we look forward to working with the agency and Congress to implement the commitment letter to the mutual benefit of biosimilar sponsors and the FDA.

We are committed to developing a robust biosimilar industry in the U.S. and to help the BsUFA program to further develop over the next five years.

We are at a critical inflection point in the biosimilars industry, and we believe that enhancing the process for biosimilar review is a critically important component to sustaining and cementing the biosimilar pathway.

But as you all know, more needs to be done outside of the BsUFA to help us all achieve our goal of lowering the cost of medicines and improving patient access to biosimilars.

To conclude, thank you for the opportunity to speak. Thank you.
[The prepared statement of Ms. Reed follows:]

Biosimilars

F O R U M

February 3, 2022 Testimony

Good morning. My name is Juliana Reed, and I am the President of the Biosimilars Forum. On behalf of the Forum members, I would like to thank you for inviting me to participate in the hearing today.

The Forum is a non-profit trade association whose mission is to educate stakeholders on the value of biosimilars and to improve access to biosimilars in the United States. Our members represent the majority of companies with the most significant U.S. biosimilars development portfolios, including: Biogen, Boehringer Ingelheim, Coherus BioSciences, Organon Inc., Pfizer Inc., Samsung Bioepis, Sandoz, Teva, and Viartis. My remarks today represent the views of our members, all of whom manufacture or market biosimilar products.

Biosimilars have the potential to provide very significant health care savings in the U.S. Although biologics represent only four percent of medicines prescribed to patients in the US, the cost of these drugs represents approximately 40 percent of total prescription drug spending. Biosimilars provide necessary competition to allow Americans access to lower-cost biologic alternatives, and their timely licensure and launch is vital to ensuring timely patient access to many life-saving or life-altering medications.

The Biosimilars Forum is supportive of the negotiated BsUFA III agreement, and we believe it represents important progress in facilitating timely access to safe and effective biosimilar medicines for patients. We are pleased the commitment letter codifies review timelines for labeling supplements, provides meeting management enhancements, and promotes best practices of communication between FDA and sponsors. These commitments will go a long way toward improving the efficiency of the biosimilar review process.

The Forum is particularly pleased that the BsUFA III program will include a regulatory science program that can help bring more biosimilars to market faster. Since the BPCIA was enacted over a decade ago, there have been many advances in the science of developing biological drugs. The regulatory science program will provide FDA and industry the ability to incorporate the latest scientific innovations into biosimilar development and regulation. It is a win-win for all.

Although we are very satisfied with the progress represented in the BsUFA III commitment letter, we want to stress that the pandemic has impacted biosimilars and patient access disproportionately hard for almost two years. We would like to ask the FDA for clarity to sponsors and the public as to the estimated timelines the FDA believes it will take to address the backlog in inspections and reviews.

Additional COVID-19 variants have stalled on-site inspections, making the situation even more uncertain. Per the Agency's May 2021 Resiliency Roadmap for FDA Inspection Oversight, biosimilar inspections are not, on their own, considered to be "mission critical" and thus are not prioritized. This has the ultimate outcome of preventing patients from quickly accessing lower cost biosimilars.

The COVID-19 related inspectional backlog has had a significant impact on biosimilars. The percentage of on-time actions for original biosimilar product applications, including resubmissions, has been unstable since the summer of 2020. On the other hand, over the past two years, on-time actions for the GDUFA and PDUFA programs have averaged over 90%; the BsUFA program, however, plunged to 75% during Quarter 4 of FY 2020, and further dropped to 67% during Quarter 1 of FY 2021. The program briefly recovered in Quarter 3, but the latest data shows another drop to 67% in Quarter 4, demonstrating unrelenting challenges for on-time action on biosimilars. This trend for biosimilar applications is markedly worse than for other user fee programs and suggests that biosimilars have been more adversely affected by pandemic-related inspectional issues. For the BsUFA III Commitment Letter to be a success and for FDA to meet its goals of first-cycle licensure of biosimilar and interchangeable products, the inspection backlog for biosimilars must be addressed.

The Forum is encouraged by FDA's commitment to hire and retain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews and applauds the agency's efforts to improve its use of data and technology. In this vein it would be very helpful for the Agency to report separately on metrics related to 351(a) "original" biologics and 351(k) "biosimilars." These metrics are currently combined, making it difficult to truly assess the FDA's performance as it relates to biosimilars.

As we head into BsUFA III we look forward to working with the Agency to implement the commitment letter to the mutual benefit of biosimilar sponsors and FDA. We are excited by the fact there is now a robust biosimilar industry, with significant development experience, to help BsUFA further develop over the next five years. We are at a critical inflection point for the biosimilars industry and we believe that enhancing the process for biosimilar review will be critically important to sustaining and cementing the biosimilar pathway for years to come, which will help us all achieve our goal of improving patient access to biosimilars.

To conclude, thank you for the opportunity to speak today. The Forum strongly supports efforts to advance a robust biosimilars program. Policies that support timely approval of biosimilars will ensure that patients have more access to high quality, safe, effective, and affordable biological therapies.

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Ms. ESHOO. Thank you.

Next, I would like to recognize Mr. David Gough. He is the Senior Vice President of Science and Regulatory Affairs at, as I said earlier, the Association for Accessible Medicines.

Welcome to you, and you have 5 minutes for your testimony, sir.

STATEMENT OF DAVID GAUGH

Mr. GOUGH. Thank you.

Chairman Eshoo, Ranking Member Guthrie, and members of the subcommittee, thank you for the opportunity to testify.

Ms. ESHOO. Move the microphone a little closer. You have a soft voice, and we want to hear everything.

Mr. GOUGH. Is that better?

Ms. ESHOO. Much better.

Mr. GOUGH. Thank you.

Thank you for the opportunity about the critical role BsUFA and GDUFA hold in increasing patient access to more affordable generic and biosimilar medicines.

My name is David Gough, Senior Vice President for Science and Regulatory Affairs at the Association for Accessible Medicines.

I am a licensed pharmacist with many years of experience in both generic and biosimilar drug industries, and I represented the industry in the initial development and in both subsequent renewals of generic and biosimilar user fee agreements.

AM and the Biosimilar Council strongly support congressional authorization of GDUFA and BsUFA as negotiated and without changes.

Timely approval of the FDA user fee agreements ensures patients will continue to benefit from new, more affordable generic and biosimilar medicines.

Over the last ten years, GDUFA and BsUFA significantly increased the resources available to the FDA for these timely reviews of applications. The benefit of this partnership between FDA and industry is clear. A record number of generic drugs were approved in 2017, again in 2018, and again in 2019, and a total of 33 biosimilars have been licensed.

A direct result of licensed competition is lowering prescription drug costs for America's patients. Since 2012, patients in the U.S. healthcare system have saved more than \$2 trillion, including \$469 billion from new generic and more than \$12 billion from biosimilars.

GDUFA III and BsUFA III build upon these successes. The user fee agreements incorporate lessons learned, including enhancements to ensure the timely review of applications and provides FDA with sufficient resources over the next five years.

GDUFA III and BsUFA III are the culmination of months of negotiation, have been subject to public review and comments, and represent a careful balance between stakeholders.

My written statement details many improvements negotiated in GDUFA III and BsUFA III, but let me highlight just a couple.

Complex generics. These are generic versions of brand-named drugs that have complex active ingredients or drug-device combinations, for example. These drugs are more difficult to develop due in part to the lack of FDA product-specific guidances.

GDUFA III includes commitments to facilitate the development and publication of these product-specific guidances for complex generics. These commitments will increase transparency and developers' understanding of FDA's expectations to allow for a more predictable review process.

Inspections. Generic and biosimilar developers support FDA's inspection program. In fact, one of the original purposes of GDUFA was to provide resources for FDA to conduct risk-based facility inspections.

GDUFA enhances the efficiencies of the inspection process by helping ensure reinspection occurs within a specified time frame.

In addition, in BsUFA III, FDA commits to issuing guidances on its use of alternate tools to request records and other documentation in lieu of inspection.

Suitability petitions. These are required to submit to the FDA when a generic drug manufacturer intends to seek approval for a drug that differs from the reference brand product. Current law requires FDA to grant or deny suitability petitions within 90 days from submission. That deadline, however, is rarely met today.

GDUFA III will enhance FDA's ability to conduct timely review of these suitability petitions with additional resources.

BLA supplements. Biosimilar developers can submit supplements to modify and approve BLA, for example, updating labeling with new safety information of changes to indications.

Under BsUFA III, FDA commits to accelerate supplement reviews for safety labels, for extrapolation for label carve-in/carveouts, and for new data.

And finally, interchangeability. As of 2022, FDA has licensed two interchangeable biosimilars. BsUFA III will help manufacturers to develop more interchangeable biosimilars to the regulatory science and demonstration projects. These demonstration projects will also evaluate mechanisms to streamline overall biosimilar development.

In closing, we strongly support timely reauthorization of GDUFA and BsUFA, and we look forward to working with members on both sides of the party to accomplish this goal.

Thank you, again, for this opportunity. I look forward to questions.

[The prepared statement of Mr. Gaugh follows:]



Testimony of
David R. Gaugh, RPh
Senior Vice President, Sciences & Regulatory Affairs
Association for Accessible Medicines

Before the
Subcommittee on Health
of the House Committee on Energy and Commerce

"FDA User Fee Reauthorization:
Ensuring Safe and Effective Drugs and Biologics"

February 3, 2022

Chairwoman Eshoo, Ranking Member Guthrie and Members of the Subcommittee:

Thank you for holding today's hearing on the reauthorization of the Food and Drug Administration's (FDA) user fee programs and for the opportunity to testify about the critical role the Generic Drug User Fee Amendments (GDUFA) and the Biosimilar User Fee Act (BsUFA) hold in increasing patient access to more affordable generic and biosimilar medicines. My name is David Gaugh, Senior Vice President for Sciences and Regulatory Affairs at the Association for Accessible Medicines (AAM). I am a licensed pharmacist with more than two decades of experience working in and around the generic drug industry, and I represented the industry in the initial development and in both subsequent renewals of the generic and biosimilar user fee agreements.

AAM and its Biosimilar Council are the nation's leading trade association for the manufacturers and distributors of FDA-approved generic and biosimilar prescription medicines. Today, generic and biosimilar medicines comprise 90% of prescriptions in the United States at only 18% of total drug spending.¹ AAM's members provide more than 52,000 jobs at nearly 150 facilities and manufacture more than 60 billion doses of generic medicines in the United States every year.² Our core mission is to improve lives by advancing timely access to high-quality, more affordable safe and effective generic and biosimilar medicines.

In today's testimony, I will highlight the success of the FDA's generic and biosimilar programs in significantly increasing patient access to lower-cost medicines and, in turn, dramatically lowering the cost of prescription drugs for America's patients and our health care system over the last 10 years; outline the improvements made to the public-private partnership embodied in GDUFA III and BsUFA III; and discuss how congressional approval of the FDA user fee programs for the next five years (FY2023-2027) will benefit patients and increase their access to more affordable treatments.

AAM and its Biosimilars Council strongly support congressional reauthorization of GDUFA and BsUFA as negotiated and without changes. Timely approval of the FDA user fee agreements ensures patients will continue to benefit from new, more affordable generic and biosimilar medicines.

GDUFA and BsUFA at 10 Years

Ten years ago, Congress created the FDA's user fee programs for generic and biosimilar medicines when it enacted GDUFA and BsUFA as part of the FDA Safety and Innovation Act of 2012. For generic drugs, the number of applications submitted to the FDA had increased substantially since enactment of the Hatch-Waxman Act. Prior to GDUFA, FDA's review of abbreviated new drug applications (ANDA) was often slow and

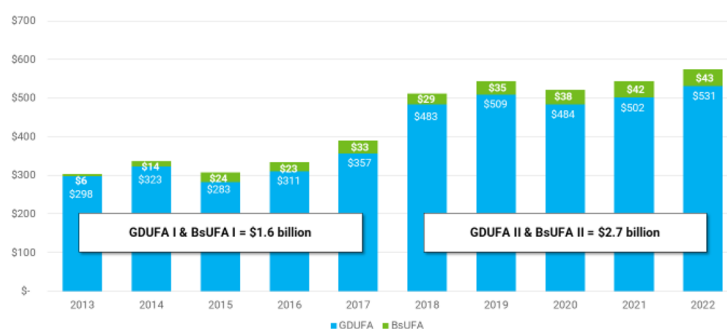
¹ AAM, "The U.S. Generic & Biosimilar Medicines Savings Report," October 2021 ([link](#)).

² AAM, "A Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain," October 2021 ([link](#)).

unpredictable. For biosimilar medicines, FDA's licensure pathway for these new treatments had been created in 2010 as part of the Biologics Price Competition and Innovation Act (BPCIA). With passage of the first GDUFA and BsUFA iterations in 2012, Congress helped ensure FDA would have sufficient resources to carry out its mission.

Congressional authorization of the FDA's generic and biosimilar user fee programs in 2012 and reauthorization in 2017 substantially increased the resources available to the Agency to review applications. More than \$4 billion in supplemental user fees from generic and biosimilar developers was and will be provided as a result.³

Generic and Biosimilar User Fee Collections CY2013-2021

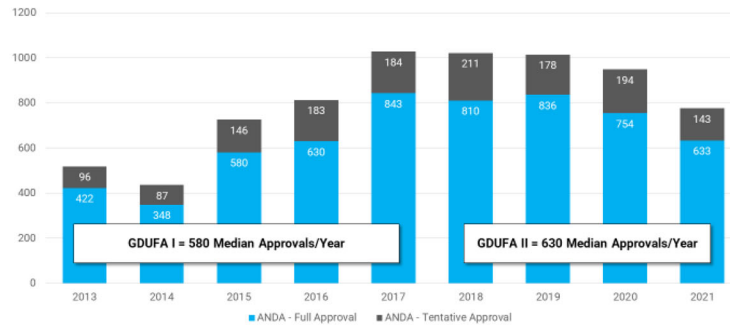


With the additional resources, FDA was able to increase efficiencies and approval of generic drugs increased significantly, with full and tentative approvals exceeding 1,000 in fiscal years 2017, 2018 and 2019. The median number of ANDA approvals has increased over time as a result of GDUFA I and GDUFA II.⁴ The partnership between FDA and the generic industry has enhanced the overall stability and predictability of the GDUFA program and accelerated the timely review of ANDAs, increasing access to quality affordable generic medicines.

³ AAM Analysis of FDA's FY2014 – FY2020 GDUFA and BsUFA Financial Reports and Five-Year Financial Plans (2021 Update). FDA's reports are available at <https://www.fda.gov/about-fda/user-fee-reports/user-fee-financial-reports>.

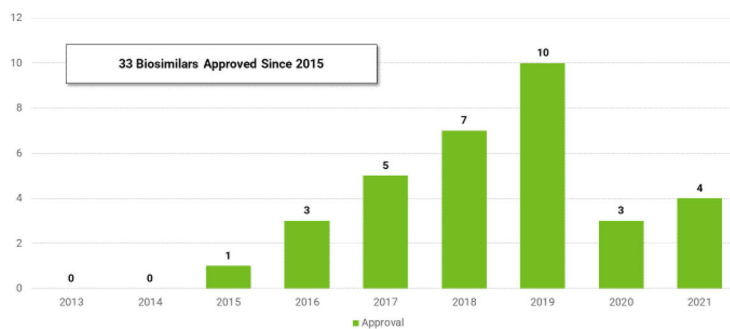
⁴ AAM Analysis of the FDA Office of Generic Drug Annual Reports (2015-2020) and Activities Report of the Generic Drug Program (FY13-FY15, FY21). FDA's reports are available at <https://www.fda.gov/drugs/generic-drugs/annual-reports>.

Generic Drug Approvals 2013-2021



Following the creation of the biosimilars pathway and subsequent development of the biosimilars program, FDA licensed the first biosimilar in 2015 and has now licensed 33 biosimilars in the U.S.⁵ Biosimilar medicines are safe, effective and more affordable treatments for patients and, with 21 products launched and available to patients, biosimilars are already delivering on their promise of lower costs and expanded patient access to care.

Biosimilar Approvals 2013-2021

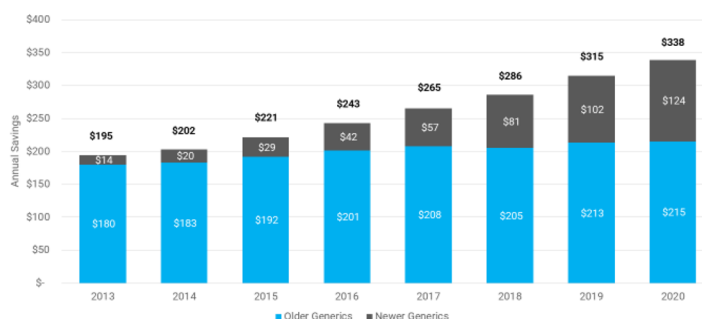


⁵ Biosimilars Council, "FDA Biosimilars Approvals," December 2021 ([link](#)).

With FDA approval, the introduction of new generic and biosimilar medicines leads to competition in the pharmaceutical market – and the result is a significant reduction in the cost of prescription drugs for patients. Experience shows drug prices decline rapidly when generics enter the market.⁶ According to FDA, prices fall as generics enter the market – by an average of 39% when there is only one generic and by nearly 80% when four or more generics enter the market.⁷ Evidence with biosimilar medicines is similar with an average cost savings of 45%.⁸ Importantly, biosimilar competition also results in lower brand biologic costs – by about 25% on average.⁹

Over the last 10 years, generics and biosimilars provided more than \$2 trillion in savings – including \$469 billion from new generics and more than \$12 billion from biosimilars – to patients and the U.S. health care system.¹⁰ In addition to the cost savings provided, patient access to life-saving treatments is broadened as the price of medicine falls. A recent analysis of Medicare Part D from the Congressional Budget Office noted “the number of standardized prescriptions dispensed for generic drugs more than doubled from 2009 through 2018.”¹¹

Annual Savings from Generics and Biosimilars (\$ Billion)



⁶ IMS Institute for Healthcare Informatics, “Price Declines after Branded Medicines Lose Exclusivity in the U.S.,” January 2016 ([link](#)).

⁷ FDA, “New Evidence Linking Greater Competition and Lower Generic Drug Prices,” December 2019 ([link](#)).

⁸ AAM Analysis of Average Sales Price Files, January 2022.

⁹ Ibid.

¹⁰ Ibid., AAM Generic & Biosimilar Savings Report.

¹¹ CBO, “Prescription Drugs: Spending, Use, and Prices,” January 2022 ([link](#)).

GDUFA and BsUFA aim to put FDA's generic and biosimilar drug programs on firm financial footing by enabling FDA to assess user fees to fund critical and measurable enhancements and, in turn, bringing greater predictability and timeliness to the review of applications. As a direct outcome, the generic and biosimilar drug programs have increased patient access to safe, effective and affordable quality medicines.

GDUFA III Enhancements

FDA plays a critically important role in making lower-cost, high-quality generic medicines available to patients. FDA reviews ANDAs submitted by generic drug manufacturers (ANDA sponsors). To receive FDA approval, data submitted in an ANDA must generally demonstrate that the generic drug is bioequivalent to the Reference Listed Drug (RLD), more commonly known as the innovator or brand product.

The GDUFA commitment letter specifies various fees the FDA sets and can collect from manufacturers, such as ANDA applications, Drug Master Files (DMF), and facility and program fees.¹² The fees paid by the generic drug industry aid FDA's ability to meet agreed-upon performance goals and commitments, such as timely reviews and other regulatory activities. FDA also provides annual reports to Congress on its performance.¹³ The increases in transparency and communication are important to FDA's ability to meet the commitments, which enhance the overall stability and predictability of the GDUFA program.

The GDUFA III negotiated commitments will further strengthen and build upon the progress made and lessons learned from GDUFA I and GDUFA II. Let me take a moment to highlight five areas – advancing approvals, complex generics, inspections, suitability petitions and sustainability – where we believe the FDA's generic drug program will be enhanced with congressional ratification of GDUFA III.

Advancing Approvals

GDUFA III includes important commitments that will maintain FDA's rigorous ANDA review standards, building upon and improving the review process to increase timely patient access to high-quality, lower-cost generic medicines. For example, the newly negotiated provision known as "imminent action" will allow the FDA to extend a goal date by up to 60 days if in FDA's judgment an approval or tentative approval of the application is imminent. This commitment will mitigate the need to add additional review cycles unnecessarily and delay approvals over minor, easily resolvable issues.

¹² AAM, "The Generic Drug User Fee Amendments (GDUFA III)," October 2021 ([link](#)); FDA, "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027," October 2021 ([link](#)).

¹³ FDA, GDUFA Performance Reports, FY2015 – FY2020 ([link](#)).

Complex Generics

Complex generics are generic versions of brand-name drugs that have complex active ingredients, routes of administration, drug-device combinations or formulations. These drugs are more difficult to develop due in part to the lack of FDA product-specific guidance. Congress and FDA helped spur competition for complex products by including provisions in the previous user fee authorizations to increase product-specific guidance publication and meetings with FDA during the product development phase. GDUFA III builds on this success through commitments to facilitate the development and publication of product-specific guidances for complex generic products – increasing transparency and understanding of FDA's expectations to allow for a more predictable review process.

Inspections

Generic and biosimilar developers support FDA's inspections program. One of the original purposes of GDUFA was to provide resources for FDA to conduct facility inspections. Under the inspections process, FDA typically inspects a facility and identifies deficiencies. The facility has a specified timeframe to address and correct the identified deficiencies and subsequently request a reinspection from FDA. In some cases, extended time passes from when a facility performs the corrective actions to resolve the deficiencies and the time period when FDA can reinspect. Delays in reinspection lead to significant delays in the review process. GDUFA III enhances the efficiencies of the inspection process by helping ensure reinspection occurs within a specified timeframe.

Suitability Petitions

Suitability petitions are required to be submitted to FDA when a generic drug manufacturer intends to seek approval of an ANDA for a drug that differs from the reference brand product in terms of the active ingredient (for a combination product), route of administration, strength and/or dosage form. Current law requires FDA to grant or deny suitability petitions within 90 days from petition submission. That deadline, however, is rarely met. This results in delays to generic market entry. GDUFA III includes commitments and resources to facilitate the FDA's ability to conduct a timely review of suitability petitions. These new resources will help FDA meet GDUFA III commitments, including conducting completeness assessments within 21 days from petition submission and using agreed upon metrics to prioritize petition reviews.

Sustainability of Resources

Under GDUFA II, FDA committed to developing a Resource Capacity Planning (RCP) capability to optimize resources and better anticipate future resource needs. GDUFA III provides an additional tool to further enhance the utility of the RCP to allow FDA to better forecast resource needs via the Capacity Planning Adjustment (CPA). The CPA will help promote sustainability for both FDA and industry by allowing FDA to increase full-time employee needs as workload increases. In turn, the CPA will provide

predictability for generic developers through a 3% cap to prevent significant fluctuation in fees and minimize the financial barriers for smaller generic manufacturers.

BsUFA III Enhancements

Similar to FDA's generic drug program, FDA helps ensure America's patients gain access to high-quality, more affordable biological products in the form of biosimilars. FDA reviews abbreviated biologics license applications (BLA) submitted by biosimilar developers. In order for a biosimilar to be licensed, data submitted in a BLA must demonstrate the biosimilar drug product is "highly similar" to the brand-name reference biologic and there are no clinically meaningful differences in safety, purity or potency.

BsUFA allowed FDA to assess and collect fees from developers and manufacturers that submit BLAs for FDA's review. The negotiated commitments enhance and improve the review process to facilitate timely access to biosimilar medicines and ensures the Agency has the necessary resources to fulfill the agreed upon commitments. FDA also provides annual reports to Congress on its performance.¹⁴

The BsUFA III negotiated agreement will further strengthen and build upon the progress made and lessons learned from BsUFA I and BsUFA II.¹⁵ Let me highlight several enhancements to FDA's biosimilars program – supplement reviews, meeting management, regulatory science and interchangeability, inspections, use of carryover funds and IT modernization. I will briefly describe each.

BLA Supplements

Biosimilar developers can submit supplements to modify an approved BLA, for example, updating labeling with new safety information or changes to indications. Under BsUFA III, FDA commits to accelerating supplement reviews for safety labels, extrapolation, label carve-in and carve-outs and new pharmacokinetic data.

Meeting Management

Biosimilar developers participate in meetings with FDA to gain insight into the agency's expectations and perspectives on different issues. These meetings help facilitate a predictable and efficient review process. BsUFA III includes commitments to: add a new type of meeting to get feedback on focused questions; make meetings more efficient; help provide FDA with sufficient information in advance of meetings; and obtain rapid clarification of meeting minutes.

¹⁴ FDA, BsUFA Performance Reports, FY2013 – FY2020 ([link](#)).

¹⁵ AAM, "Key Elements of BsUFA III," September 2021 ([link](#)); FDA, "Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027," September 2021 ([link](#)).

Regulatory Science and Interchangeability

As of January 2022, FDA has licensed two interchangeable biosimilars. In order to achieve the interchangeable designation, a biosimilar must produce the same clinical result as the brand-name biologic. With the interchangeable designation and subject to state law, a pharmacist may dispense an interchangeable biosimilar when a brand-name biologic is prescribed without intervention from the provider. BsUFA III will help manufacturers to develop more interchangeable biosimilars through the new Regulatory Science Program's demonstration project. These demonstration projects will also evaluate mechanisms to streamline overall biosimilar development. Findings from the demonstration projects will inform a comprehensive strategy to advance interchangeability and the development of future guidance documents.

Remote Inspections

FDA uses alternate tools to conduct inspections and supplement its ability to assess manufacturing facilities remotely. Due to the COVID-19 pandemic, FDA used these alternate tools to request records and documentation from its regulatory partners. Under BsUFA III, FDA commits to issuing guidance on the use of alternative tools.

Use of Carryover Funds

Any remaining user fees collected by FDA but not yet spent are carried over to the next year. Under BsUFA III, FDA commits to reducing the carryover balance from 39 weeks to 21 weeks over a three-year period.

IT Modernization

FDA continues to modernize the Agency's IT capabilities. BsUFA III will further FDA's efforts. For example, FDA will modernize and move the Electronic Submissions Gateway to the cloud to help improve transparency and communication.

Conclusion

Patient access to generic and biosimilar medicines has never been more critical. Over the last 10 years, GDUFA and BsUFA significantly increased the resources available to FDA for review of generic and biosimilar applications. The benefit of this partnership between FDA and industry is clear: record levels of generic drugs were approved in 2017-2019 and more than 30 biosimilar medicines were licensed. The end result is lower prescription drug costs for America's patients. Since the establishment of FDA's generic and biosimilar programs in 2012, patients and the U.S. health care system have saved more than \$2 trillion – including \$469 billion from new generics and more than \$12 billion from biosimilars. Congressional passage of GDUFA and BsUFA, along with their reauthorization in 2017, made this possible.

GDUFA III and BsUFA III build on this success. The user fee agreements incorporate lessons learned, include enhancements to ensure the timely review of applications and provide FDA with sufficient resources over the next five years (FY23-27). GDUFA III and BsUFA III are the culmination of months of negotiations, have been subject to public review and comment, and represent a careful balance between stakeholders. AAM and its Biosimilars Council strongly support congressional reauthorization of GDUFA and BsUFA as negotiated and without changes. Timely approval of the FDA user fee agreements ensures patients will continue to benefit from new, high-quality and more affordable generic and biosimilar medicines. We look forward to working with members of both parties to accomplish this goal.

Thank you again for the opportunity to testify on this important issue. I look forward to answering your questions.

Ms. ESHOO. Thank you very much, Mr. Gaugh.

And last but not least, Dr. Ramachandran, your 5 minutes of testimony.

STATEMENT OF RESHMA RAMACHANDRAN, M.D.

Dr. RAMACHANDRAN. Chairwoman Eshoo, Ranking Member Guthrie, and distinguished members of the subcommittee, thank you for the invitation to testify today.

My name is Reshma Ramachandran. I am a physician and a researcher in the National Clinician Scholars Program at Yale School of Medicine. I also lead the Doctors for America FDA Task Force, which is an independent group of physicians working together to support and strengthen the FDA to ensure medical products meaningfully improve clinical outcomes for our patients.

I am honored to testify before you today. My remarks reflect my own views and not that of my employer nor the organizations I work with.

Taking care of patients amid an ongoing devastating pandemic has reinforced the critical role of the FDA in protecting our patients and our Nation's public health. The agency has not only enabled the availability of multiple proven vaccines, drugs, and diagnostics, but has also been continuously evaluating rapidly emerging evidence to make scientifically driven regulatory decisions that ensure their appropriate use.

While COVID-19 has certainly highlighted the need for the FDA and its strengths, other recent events, including the controversial approval of the Alzheimer's disease drug Aducanumab, have exposed how the agency has faltered, especially when putting industry and insurance before that of patients.

The proposed user fee agreements reflect this tension. On one hand, as a clinician I do want to make sure that the FDA regulatory review process is as efficient as possible so that my patients have timely access to new treatments and vaccines.

This means ensuring adequate funding for hiring and retaining staff to review the growing number of drug and biologic applications submitted to the FDA for approval and for the agency to be nimble in shifting personnel and resources when confronted with a public health emergency, a key priority that is included within the proposed user fee legislation.

Conversely, the FDA has been increasingly approving new medications more quickly and based on lesser best evidence. This has left our patients and us as prescribers with greater uncertainty around whether these approved products are truly clinically beneficial and safe.

With accelerated approval, the expedited review pathway by which Aducanumab was approved, FDA struck a bargain with industry sponsors, in allowing for approval to be expedited through smaller, shorter clinical trials that used surrogate endpoints that are hypothesized to be associated with clinically meaningful outcomes.

In exchange, industry sponsors are required to conduct trials after approval that confirm clinical benefits. However, industry has not upheld their end of the bargain. Since accelerated approval was introduced in 1992, almost half of the drugs approved through this

pathway have not yet been confirmed to be clinically beneficial for patients as of 2020.

Of these, one-fifth have remained available for patients to use for more than five years. Even when the completed post-approval trials have failed to confirm the drug's clinical benefit, the FDA has either delayed withdrawing or not withdrawn these approvals.

Both this prolonged uncertainty of these drugs' clinical benefit as well as the FDA allowing them to be prescribed even after they failed confirmatory trials harms patients both medically and financially.

As in Europe and other countries, the FDA should require manufacturers to renew accelerated approval on a yearly basis and submit interim reports on their progress in completing mandated confirmatory trials. If they fail to do so, the approval should expire.

Additionally, should a confirmatory trial show negative results, the indication approvals should be automatically withdrawn.

Moreover, the FDA should also require sponsors receiving accelerated approval to finalize their confirmatory trial protocols with agency officials, preventing any delays in initiating such trials.

The FDA must also improve the quality of these trials by requiring them to use clinical endpoints, not surrogate endpoints, especially those that are unvalidated or were used as the basis of the initial approval.

Moreover, one study found that none of the 50 confirmatory trials mandated by the FDA for recent accelerated approvals could be feasibly emulated using real world data, making real world data currently an unlikely source of reliable evidence to replace post-approval confirmatory trial requirements, as has been proposed in other legislation.

Additionally, the user fee agreements include several agency review metrics that the FDA will be reporting on regarding their success in expediting approvals.

However, the FDA should develop and publicly report other more meaningful clinical metrics for patients and clinicians. For instance, how many new drugs and biologic medicines were approved even though the primary clinical trial endpoint was not met, as with Aducanumab?

Our preliminary findings suggest that this might be as high as ten percent in recent years.

Another example, for how many accelerated approvals were benefits confirmed post approval?

If such metrics are not included, the FDA will continue to focus its efforts towards reaching industry-driven benchmarks instead of those that are patient centered.

In my written testimony, I have outlined other opportunities through the proposed user fee legislation to ensure a strong, independent FDA that will also instill public trust in its important work.

I am happy to answer any other questions you might have. Thank you, again, for this opportunity.

[The prepared statement of Dr. Ramachandran follows:]

Written Testimony of Reshma Ramachandran, M.D., M.P.P. of Yale School of Medicine

Hearing on “FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics”
 Subcommittee on Health
 U.S. House of Representatives Committee on Energy and Commerce
 February 3, 2022

Chairman Pallone, Ranking Member Rodgers, and distinguished members of the subcommittee, thank you for the invitation to testify today. My name is Reshma Ramachandran. I am a researcher and a fellow in the National Clinician Scholars Program at Yale School of Medicine. I also serve our nation’s veterans as a primary care physician at the West Haven Veterans Affairs Medical Center. Additionally, I lead the Doctors for America Food and Drug Administration (FDA) Task Force, which is an independent group of physicians across specialties who provide unbiased expertise in evaluating and responding to the FDA regulatory process in a way that maximizes meaningful clinical outcomes for our patients. I am honored to testify before you today. My remarks reflect my own views and not that of my employers nor the organizations I work with.

The past two years of living in continued uncertainty amid an ongoing pandemic has reinforced the critical role of the FDA in protecting patients and public health. The agency has not only enabled the market entry of multiple proven vaccines, drugs, and diagnostics, but has continuously evaluated rapidly emerging evidence related to these health technologies to make scientifically driven regulatory decisions to ensure their appropriate use. While COVID-19 has certainly highlighted the need for and the strengths of the FDA, other recent events have also confirmed the need for urgent reforms.¹

As this committee is well aware, the FDA recently and controversially granted accelerated approval to aducanumab, a costly treatment approved for early-stage Alzheimer’s disease based on an unvalidated surrogate endpoint.² The FDA proceeded forward with this approval despite concerns raised by multiple experts including those on the agency’s own independent advisory committee around its significant safety risks. While this unusual approval is concerning enough by itself, it has also exposed other longstanding, problematic practices at the FDA that must be addressed if the agency is to fulfill its mission of “protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological medicines, and medical devices.”³

In this written testimony, I will outline the importance of maintaining a strong FDA, specific aspects of the proposed user fee agreements that are essential for improving the health of

¹ Gonsalves G, Morten C, Ramachandran R, Ross JS. Opinion | The FDA is in desperate need of some soul-searching. *Washington Post*. <https://www.washingtonpost.com/opinions/2021/06/17/fda-aducanumab-alzheimers-drug-approval-erodes-confidence/>. Published June 17, 2021.

² Ramachandran R, Ross JS. New Alzheimer’s drug sets dangerous precedent. *CNN Opinion*. Published online June 17, 2021. <https://www.cnn.com/2021/06/17/opinions/biogen-alzheimers-drug-opinion-ramachandra-ross/index.html>

³ Food and Drug Administration. What We Do. *FDA*. Published June 28, 2021. Accessed January 31, 2022. <https://www.fda.gov/about-fda/what-we-do>

patients, and opportunities for Congress to consider additional safeguards as part of these agreements in order to uphold and support an agency vital to our nation's public health.

The FDA's regulatory decision-making process is essential for my patients and for my clinical practice.

For clinicians like me, FDA approval of a drug or biologic medicine signals that the approved medical product is safe and effective to be prescribed to patients. With FDA approval comes the understanding that the agency has required and reviewed data collected from well-designed clinical trials testing the drug in patients like mine before determining that these new treatments are indeed, safe and effective. It also gives reassurance that the FDA has done its due diligence in certifying that the manufacturing processes for these medications are safe and of high quality.

The FDA also contributes to creating an enabling environment for robust health technology development. The agency routinely provides guidance to drug developers and manufacturers regarding regulatory standards for medical product approval and works closely with sponsors throughout the submission and application review process. Moreover, the agency also awards several incentives to drug manufacturers to motivate the research and development of novel products for unmet medical needs. This can include designations for special regulatory programs⁴ that expedite the regulatory review process or that allocate FDA resources including staff to shorten clinical development times as well as intellectual property protections in the form of exclusivity periods upon approval.⁵

The FDA also plays an oversight role during the regulatory review process in analyzing the data generated from clinical trials. The agency has the authority to issue holds on studies if the drug being tested is suspected to cause potential adverse effects or if standards for good clinical trial conduct are not being upheld. Even after the drug has been allowed onto the market, the FDA continues to monitor safety and efficacy of treatments. Such ongoing surveillance is especially critical for protecting patients as the FDA increasingly approves new drugs and biological medicines based on less robust evidence in exchange for earlier access to these treatments.^{6,7} This continuous monitoring has led the agency to make rapid, evidence-based

⁴ Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. *FDA*. Published June 15, 2019. Accessed January 31, 2022. <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review>

⁵ Food and Drug Administration. Frequently Asked Questions on Patents and Exclusivity. *FDA*. Published online February 5, 2020. Accessed January 31, 2022. <https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity>

⁶ Medicine I of. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. (Baciu A, Stratton K, Burke SP, eds.). The National Academies Press; 2007. doi:[10.17226/11750](https://doi.org/10.17226/11750)

⁷ Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017. *JAMA Network Open*. 2020;3(4):e203284. doi:[10.1001/jamanetworkopen.2020.3284](https://doi.org/10.1001/jamanetworkopen.2020.3284)

decisions in the form of warning letters or withdrawals of marketed medical products to protect patients from further harm.

The FDA also translates the underlying rationale behind their complex regulatory decisions to both patients and clinicians through several different avenues. This includes public hearings with independent experts, regulatory review summary documents, publications in medical journals, public testimony to elected officials, educational briefings, prescriber alerts, public newsletters, and press releases. The agency also uses social media and other traditional media avenues to broadly communicate their activities and decisions.

At the start of the pandemic, the FDA quickly pivoted to address the ongoing public health emergency of COVID-19, redirecting resources and personnel, and engaging independent experts to hasten the robust development and availability of COVID-19 diagnostics, vaccines, and therapeutics. The agency established the Coronavirus Treatment Acceleration Program (CTAP) to support clinical trials testing new treatments and vaccines for COVID-19.⁸ They also partnered closely with other agencies including the National Institutes of Health (NIH) as part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, providing expertise around clinical trial design and conduct as well as regulatory standards for authorization and approval. The FDA has also made strides during the ongoing pandemic to increase transparency around their emergency use authorization recommendations and regulatory decisions related to COVID-19. This has helped promote public confidence in their scientific review process and to ensure that clinicians and patients are made aware of how to appropriately use COVID-19 health technologies.

Like many of my colleagues, I have concerns that the increasing reliance on user fees from the very industry that the FDA regulates has unduly impacted regulatory standards creating further unnecessary flexibility for manufacturers in the regulatory review and approval process.⁹ Increasingly, the agency has expedited the approval of drugs and biological medicines, which has been found to be associated with less robust clinical trial evidence and more uncertainty of these treatments' clinical benefit. I firmly believe that in order for the FDA to maintain its independence as a national regulatory authority tasked with protecting public health that Congress should be appropriating further funding to the agency, thereby reducing its dependence on industry actors and mitigating undue influence that fails to prioritize patients. Nevertheless, in the absence of sufficient funding for the FDA to maintain its current operations as well as to address its growing footprint on our healthcare system, Congress should intervene to ensure that these user fee agreements include safeguards to protect patients and public health.

⁸ Food and Drug Administration. Coronavirus Treatment Acceleration Program (CTAP). *FDA*. Published January 7, 2022. Accessed January 31, 2022. <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>

⁹ Darrow JJ, Avorn J, Kesselheim AS. Speed, Safety, and Industry Funding — From PDUFA I to PDUFA VI. *New England Journal of Medicine*. 2017;377(23):2278-2286. doi:[10.1056/NEJMp1710706](https://doi.org/10.1056/NEJMp1710706)

The Prescription Drug User Fee Authorization (PDUFA),¹⁰ Generic Drug User Fee Authorization (GDUFA),¹¹ and Biosimilar User Fee Authorization (BsUFA)¹² Acts funds important operations at the FDA as well as other urgently needed priorities.

The creation of new and unexpected workstreams dedicated to COVID-19 has required the use of further resources and funding for the hiring of additional staff to ensure timely review of urgently needed diagnostics, vaccines, and therapeutics. Moreover, as shown within the annual PDUFA Performance reports, sponsors have been submitting an increasing number of new drug approval (NDA) and biologics license approval (BLA) applications.¹³ Most of these submissions were also for new drugs and biologics that received expedited review pathway designations including priority review, which requires the FDA to complete their review process in six months rather than the standard 10 months. In 2020, the FDA received 56% more submissions for original priority NDAs and BLAs compared to the 5-year average of the number of such submissions received between 2015 and 2019.¹⁴

For the FDA to be able to rigorously review a growing number of NDAs and BLAs, user fees have been proposed to pay for hiring additional staff support as well as to retain current staff. Ensuring that the FDA has sufficient staff to continue its critical role in assessing medication efficacy and safety will also allow the agency to be nimble, particularly when faced with unanticipated public health threats. Additionally, the FDA has committed to further streamlining the process for generic and biosimilar drug review, which may allow for more timely patient access to more affordable generic and biosimilar alternatives to costly brand-name drugs and biologics.

The FDA has also committed to taking a stepwise, thoughtful approach in the adoption of novel evidence generation through real-world evidence (RWE) studies and other complex clinical trial designs. Such careful evaluation will be necessary to determine whether such methods are not just more efficient, but also sufficient in making regulatory decisions. Finally, the FDA has also pledged to strengthen safety surveillance efforts including the Sentinel Initiative, increase its public availability, and enhance its capability to conduct analyses of specific safety issues. This will help to advance safety signal evaluations so that the agency can take more timely action and prevent drug-related adverse events.

¹⁰ *Prescription Drug User Fee Amendments of 2022*; 2022. Accessed January 31, 2022.

https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/PDUFA-title_01_xml_1.pdf

¹¹ *Generic Drug User Fee Amendments of 2022*; 2022. Accessed January 31, 2022.

https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/GDUFA-title_01_xml_1.pdf

¹² *Biosimilar User Fee Amendments of 2022*. Accessed January 31, 2022.

https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BsUFA-title_01_xml_1.pdf

¹³ Food and Drug Administration. FY 2020: Performance Report to Congress for the Prescription Drug User Fee Act. Published online 2020. <https://www.fda.gov/media/151602/download>

¹⁴ *Id*

The user fee agreements offer several opportunities for Congress to further strengthen the FDA regulatory review process and make it more patient-centered in order to ensure timely access to drugs and biologic medicines proven to be truly effective and safe.

Reforms to that end include:

Including More Clinically Meaningful, Patient-Centered Measures of FDA's Performance

As part of the user fee agreements, the FDA has put forward a number of performance goals and metrics related to timely agency review of and action on drug and biologic medicines submissions. While laudable that FDA is making efforts to increase its efficiency in reviewing applications, the agency should also measure more clinically meaningful and patient-centered measures of its performance.¹⁵ Examples of such measures include:

- the percentage of NDAs and BLAs approved for which prespecified primary endpoints within pivotal trials were missed (our research examining this frequency in a subset of drugs and biologic medicines showed that primary endpoints were missed in approximately one in 10 FDA approved drugs¹⁶; for aducanumab, in only one of two pivotal clinical trials, which were halted due to futility, was the prespecified endpoint met by a very small, clinically irrelevant margin¹⁷);
- the percentage of NDAs and BLAs for which FDA approval decisions were concordant with the recommendations of the agency's independent advisory committees (prior studies have found that 22% of FDA's approval decisions were discordant with recommendations from its advisory committees with the agency making more restrictive decisions in a majority of these instances than what had been recommended by the advisory committee¹⁸);
- the percentage of NDAs and BLAs approved with postmarketing requirements where those mandatory studies have been fulfilled and have demonstrated positive results in confirming the drugs' efficacy and safety (prior research has found that even five or six years after approval, a significant proportion of studies remain uncompleted or have yet to be initiated¹⁹); and
- the percentage of NDAs and BLAs approved for which the FDA later withdrew or issued warnings based on completed postmarketing studies (an earlier study of therapies approved by the FDA between 2001 and 2010 found that nearly a third were affected by a

¹⁵ Abrams M. Comments Regarding the Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments; Docket No. FDA-2021-N-0891. Published online October 28, 2021. Accessed January 31, 2022. <https://www.citizen.org/wp-content/uploads/2606.pdf> (Public Citizen has been proposing such measures as public stakeholders to the FDA PDUFA VII Reauthorization Meetings)

¹⁶ *Ongoing work*

¹⁷ Alexander GC, Knopman DS, Emerson SS, et al. Revisiting FDA Approval of Aducanumab. *New England Journal of Medicine*. 2021;385(9):769-771. doi:[10.1056/NEJMp2110468](https://doi.org/10.1056/NEJMp2110468)

¹⁸ Zhang AD, Schwartz JL, Ross JS. Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008–2015. *The Milbank Quarterly*. 2019;97(3):796-819. doi:[10.1111/1468-0009.12403](https://doi.org/10.1111/1468-0009.12403)

¹⁹ Woloshin S, Schwartz LM, White B, Moore TJ. The Fate of FDA Postapproval Studies. *New England Journal of Medicine*. 2017;377(12):1114-1117. doi:[10.1056/NEJMp1705800](https://doi.org/10.1056/NEJMp1705800)

postmarket safety event – either withdrawal, FDA issuance of boxed warnings, or FDA issuance of safety communications²⁰).

Furthermore, ensuring evaluation of more patient-centered, clinically meaningful metrics could prompt the FDA to make commitments around their regulatory review processes that benefit patients, not just industry sponsors. Without such measurement, the FDA will focus its efforts and resources to reaching benchmarks primarily toward hastening regulatory review of health technologies without ample consideration of whether its stated mission of also ensuring that these medical products are also “more effective, safer, and more affordable”²¹ is being achieved.

Revisiting Evidentiary Standards for Drugs and Biologics Approved Through Expedited Review Pathways

While expedited review pathways such as the accelerated approval pathway have allowed for patients to access drugs earlier based on surrogate endpoints instead of clinical endpoints, it has come with the tradeoff of continued uncertainty of their clinical benefit. Under accelerated approval, the FDA mandates the completion of additional studies after approval to confirm the drugs’ and biologics’ hypothesized clinical benefit within a certain time period. Contingent on the coverage decision made by payors, the accelerated approval therapeutic can be prescribed by clinicians and made available to patients for use upon approval and before the completion of these confirmatory trials. When these studies are completed, the FDA reviews the confirmatory trial data to determine whether these drugs would be eligible for standard approval.

An analysis by *The BMJ* of 253 drugs approved through the accelerated approval pathway between 1992 and 2020 found that nearly half of the drugs (n=112) have not been confirmed to be clinically effective.²² Of these drugs without confirmatory evidence of their clinical benefit, one-fifth (n=24) have been on the market for more than five years. Only sixteen of all accelerated approval drugs from this period were withdrawn, either due to a lack of efficacy or because the confirmatory trials were never conducted.

In the case of aducanumab, the FDA has given Biogen a gratuitous nine years to complete their confirmatory trials, which is much longer than the median postapproval trial duration or results reporting deadline for other accelerated approval drugs.²³ However, for other

²⁰ Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA*. 2017;317(18):1854-1863. doi:[10.1001/jama.2017.5150](https://doi.org/10.1001/jama.2017.5150)

²¹ Food and Drug Administration. What We Do. About FDA. Published June 28, 2021. Accessed January 31, 2022. <https://www.fda.gov/about-fda/what-we-do>

²² Mahase E. FDA allows drugs without proven clinical benefit to languish for years on accelerated pathway. *BMJ*. 2021;374:n1898. doi:[10.1136/bmj.n1898](https://doi.org/10.1136/bmj.n1898)

²³ Wallach JD, Ramachandran R, Bruckner T, Ross JS. Comparison of Duration of Postapproval vs Pivotal Trials for Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval, 2009-2018. *JAMA Network Open*. 2021;4(11):e2133601. doi:[10.1001/jamanetworkopen.2021.33601](https://doi.org/10.1001/jamanetworkopen.2021.33601)

accelerated approval drugs, long delays in completing required confirmatory trials have also been described.²⁴ The FDA has also waived postapproval trial requirements for some drugs despite accelerated approval being conditioned on completion of further studies to demonstrate clinical benefit.²⁵

Even when these required confirmatory trials are conducted and show negative results, the FDA has failed to withdraw indication approvals. In April 2021, FDA's Oncologic Drugs Advisory Committee (ODAC) reviewed confirmatory evidence for six oncology indications that had earlier received accelerated approval.²⁶ Despite some of these drugs failing to confirm clinical benefit in their postmarket studies, ODAC voted to maintain their approval. While the FDA could make a regulatory decision that differs from the recommendations of advisory committees, this rarely occurs.²⁷

Finally, postmarket confirmatory clinical trials required for accelerated approval drugs continue to rely on surrogate endpoints despite the intention for the trial to confirm clinical benefit and their initial approval having been based on a surrogate endpoint. In one study looking at cancer drugs approved by the FDA between 1992 and 2017 through the accelerated approval pathway, over 40% used a surrogate endpoint as the basis for confirming benefit. Of these, nearly one-half used the same surrogate endpoint as the associated preapproval pivotal clinical trial.²⁸ Additionally, postmarket confirmatory studies for accelerated approval drugs are also small and short, with many lacking randomization, blinding, or concurrent controls²⁹ – key characteristics of well-designed clinical trials.

As part of these user fee agreements, the FDA should commit to revisiting evidentiary standards for approval through expedited pathways such as accelerated approval. First, the FDA should not allow for accelerated approvals to continue forward in perpetuity. The FDA could withdraw accelerated approval indications if postapproval confirmatory trials are significantly delayed or fail to show clinical benefit,³⁰ but this can a lengthy process involving a public

²⁴ Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636. doi:[10.1001/jama.2017.9415](https://doi.org/10.1001/jama.2017.9415)

²⁵ Gyawali B, Ross JS, Kesselheim AS. Fulfilling the Mandate of the US Food and Drug Administration's Accelerated Approval Pathway: The Need for Reforms. *JAMA Internal Medicine*. 2021;181(10):1275-1276. doi:[10.1001/jamainternmed.2021.4604](https://doi.org/10.1001/jamainternmed.2021.4604)

²⁶ Powell K, Lythgoe MP, Prasad V. The Oncologic Drugs Advisory Committee Votes of April 2021—Implications for the Fate of Accelerated Approval. *JAMA Oncology*. 2021;7(11):1607-1609. doi:[10.1001/jamaoncol.2021.3046](https://doi.org/10.1001/jamaoncol.2021.3046)

²⁷ Zhang AD, Schwartz JL, Ross JS. Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008–2015. *The Milbank Quarterly*. 2019;97(3):796-819. doi:[10.1111/1468-0009.12403](https://doi.org/10.1111/1468-0009.12403)

²⁸ Gyawali B, Hey SP, Kesselheim AS. Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval. *JAMA Internal Medicine*. 2019;179(7):906-913. doi:[10.1001/jamainternmed.2019.0462](https://doi.org/10.1001/jamainternmed.2019.0462)

²⁹ Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration.

³⁰ Beaver JA, Pazdur R. “Dangling” Accelerated Approvals in Oncology. *New England Journal of Medicine*. 2021;384(18):e68. doi:[10.1056/NEJMp2104846](https://doi.org/10.1056/NEJMp2104846)

hearing should the sponsor not voluntarily withdraw the indication.³¹ During this time, the drug remains available for patients despite continued uncertainty of its clinical benefit or even when postapproval trials show negative results, as with the six indications considered by the FDA's ODAC in late April 2021.

Regulatory authorities in other countries including the United Kingdom, Australia, and Europe who award similar such approvals allow them to expire and require renewal of these conditional approvals every one to two years.³² As part of the renewal process, sponsors must submit an interim report on any outstanding obligations including timelines for completion of confirmatory trials. The FDA should adopt a similar approach to ensure more timely completion of confirmatory clinical trials, which could thereby mitigate potential clinical and financial harms for patients should the drug fail to demonstrate meaningful benefit. Regardless, should the confirmatory trials demonstrate negative results, the FDA should also automatically withdraw accelerated approval instead of waiting to convene advisory committee members for further discussion or relying on manufacturers to voluntarily withdraw these indications.³³

Coupled with these steps, the FDA should adopt similar practices from its COVID-19 initiatives in investing in educational efforts to inform patients and clinicians when accelerated approval is granted for a new drug and that it may be possible for the drug could be withdrawn should confirmatory trials fail to show clinical benefit for patients. Clear and ongoing communication about the regulatory review process will help mitigate any possible treatment disruptions if the indication is removed.

Moreover, the FDA should require that confirmatory trials for accelerated approval drugs use clinical endpoints, not surrogate endpoints, especially when the surrogate endpoints used in the preapproval clinical trials are unvalidated and without a proven association with clinical outcomes. Finally, the FDA should also mandate that for sponsors to receive accelerated approval that confirmatory trial protocols must be discussed and finalized with agency officials in order to verify that the trials are well-designed and for the sponsors to begin enrollment as soon as the drug is approved, thereby preventing against any delays in initiating such trials. These reforms will ensure that the FDA achieves the intent of the accelerated approval pathway of ensuring patients timely access to treatments are truly promising, not just wishful thinking.³⁴

³¹ *Food and Drug Administration Safety and Innovation Act*, Vol 301.; 2012.

<https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf>

³² Mehta GU, de Claro RA, Pazdur R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. *JAMA Oncology*. Published online January 20, 2022. doi:[10.1001/jamaoncol.2021.6854](https://doi.org/10.1001/jamaoncol.2021.6854)

³³ Gyawali B, Ross JS, Kesselheim AS. Fulfilling the Mandate of the US Food and Drug Administration's Accelerated Approval Pathway: The Need for Reforms. *JAMA Internal Medicine*. 2021;181(10):1275-1276. doi:[10.1001/jamainternmed.2021.4604](https://doi.org/10.1001/jamainternmed.2021.4604)

³⁴ *Id*

Using Real-World Evidence Appropriately and Transparently for Regulatory Decision-making

Increasingly, the FDA has been examining the quality and acceptability of real-world evidence (RWE) for regulatory decision-making as mandated under the 21st Century Cures Act, particularly for supporting new indication approvals of approved drugs or satisfying postapproval study requirements. Legislative proposals have also emerged to allow the use of real-world data (RWD) including patient registries, electronic health records, medical claims, and digital health technologies to fulfill postapproval confirmatory trial study requirements for accelerated approval drugs.³⁵ Within the proposed user free agreements, the FDA has committed to initiating the Advanced Real-World Evidence Pilot Program where the agency will work closely with a small group of sponsors in designing a RWE study using RWD in support of a proposed regulatory decision.

Recent research has raised questions on the feasibility of using RWD to support certain regulatory decisions. One study found that only 15% of US-based clinical trials published in high-impact medical journals could be feasibly replicated using the RWD sources of administrative claims or electronic health records data.³⁶ Another study examined whether it would be feasible to use such data to emulate FDA-required postapproval confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.³⁷ Of the 50 confirmatory trials required by the FDA for these drugs, none could be feasibly emulated using currently available RWD in terms of medical claims or structured electronic health record data. This suggests that currently available RWD and observational methods are unlikely to replace postapproval confirmatory trial requirements as has been proposed.

When RWD has been used to emulate randomized controlled trials, it has underscored several complexities in designing such studies. One recently published study used medical claims data to emulate a randomized controlled trial examining the cardiovascular risk of prostate cancer treatment.³⁸ Only one-quarter of real-life patients using the tested treatments met the randomized controlled trial's narrow inclusion and exclusion criteria. Additionally, the study authors were unable to use RWD to precisely emulate the endpoints examined within the randomized-controlled trial. Other considerations for designing such studies include the ability to assess follow-up with available RWD as well as appropriate statistical analyses as such data is not as well controlled as in traditional clinical trials.

³⁵ DeGette D, Upton F. *Discussion Draft: Cures 2.0 Act.*; 2021:127.

https://degette.house.gov/sites/degette.house.gov/files/Cures%202.0_DISCUSSION%20DRAFT.pdf

³⁶ Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. *JAMA Network Open*. 2019;2(10):e1912869. doi:[10.1001/jamanetworkopen.2019.12869](https://doi.org/10.1001/jamanetworkopen.2019.12869)

³⁷ Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. *JAMA Network Open*. 2021;4(11):e2133667. doi:[10.1001/jamanetworkopen.2021.33667](https://doi.org/10.1001/jamanetworkopen.2021.33667)

³⁸ Wallach JD, Deng Y, McCoy RG, et al. Real-world Cardiovascular Outcomes Associated With Degarelix vs Leuprolide for Prostate Cancer Treatment. *JAMA Network Open*. 2021;4(10):e2130587. doi:[10.1001/jamanetworkopen.2021.30587](https://doi.org/10.1001/jamanetworkopen.2021.30587)

Although the FDA is taking steps to carefully understand these complexities to identify appropriate study designs and characteristics for using RWD, the agency should invest in further research with public stakeholder engagement to clearly outline appropriate use conditions for RWD in making regulatory decisions. This should be done ahead of further statutory mandates that may preclude the agency's scientific and public health discretion in determine where RWE has been shown to benefit patients. Moreover, just as sponsors of clinical trials are required under law to publicly register their studies, submit trial protocols, and report results information on ClinicalTrials.gov,³⁹ sponsors of RWE studies should also do the same. This practice of transparency should be initiated as part of the Advancing RWE Pilot Program to allow for further independent expertise in determining appropriate use of such studies toward regulatory decision-making.

Ensuring Timely Completion and Integrity of Postmarketing Studies

Increasingly, the FDA is approving drugs and biologic medicines through expedited review pathways supported by fewer pivotal clinical trials that are smaller, shorter, and more often evaluating surrogate endpoints compared to those approved through standard pathways.⁴⁰ With treatments being approved based on trials with less rigorous study design, it has become increasingly important for the FDA to require postmarket studies to continue to evaluate their safety and efficacy after approval. However, studies have found that many sponsors either fail to complete or even initiate required postmarketing studies. One study found that of the postmarketing requirements and commitments issued by the FDA in 2009 and 2010, nearly 20% have not even been started, 25% were delayed or ongoing, and just over 50% had been completed five to six years after approval.⁴¹ Such delays have also been seen for accelerated approval drugs where approval is conditioned on the completion of required postapproval confirmatory studies; in a study of drugs granted accelerated approval by the FDA between 2009 and 2013, only approximately two-fifths of these drugs were found to have confirmatory evidence of efficacy in postmarket trials within 3 years of approval.⁴²

Additional studies examining required postmarketing studies found that the median times allowed by the FDA for sponsors to submit protocols for clinical trials ranged widely between

³⁹ National Institutes of Health, Department of Health and Human Services. *PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION*; 2017. Accessed August 17, 2021. <https://www.ecfr.gov/>

⁴⁰ Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017. *JAMA Netw Open*. 2020;3(4):e203284. doi:[10.1001/jamanetworkopen.2020.3284](https://doi.org/10.1001/jamanetworkopen.2020.3284)

⁴¹ Woloshin S, Schwartz LM, White B, Moore TJ. The Fate of FDA Postapproval Studies. *New England Journal of Medicine*. 2017;377(12):1114-1117. doi:[10.1056/NEJMp1705800](https://doi.org/10.1056/NEJMp1705800)

⁴² Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636. doi:[10.1001/jama.2017.9415](https://doi.org/10.1001/jama.2017.9415)

three and 15 months.⁴³ Moreover, the authors also found that the median times permitted for the sponsor to complete the required study following protocol submission were two to 13 times longer than the time required for primary outcome ascertainment; accelerated approval drugs were also noted to have approximately two years longer than the time required for primary outcome ascertainment. These findings suggest that the FDA should shorten the time allotted for required postmarket study protocol submission, study initiation, and trial completion in addition to the stated agency goals within the proposed user fee agreements of identifying and communicating anticipated postmarketing requirements to sponsors ahead of approval.

***Maintaining Rigorous Standards for Approval for Therapeutics for Diseases of Unmet Need
Cell and Gene Therapies***

Within the proposed user fee agreements, the FDA has committed to enhancing the Cell and Gene Therapy Program to facilitate more timely development and availability of novel cell and gene therapies. The agency has stated that it will further expand this program through increased staff support and continued engagement with stakeholders around novel development approaches as well as the use of real-world evidence as confirmatory evidence of clinical benefit.

In a recent study, we examined the five novel gene therapies that have received FDA approval as of December 31, 2020.⁴⁴ We found that through the regenerative medicine advance therapy (RMAT) designation, the FDA has been able to successfully expedite the development and market entry of these products. In fact, their median clinical development period was substantially faster than that of traditional pharmaceutical products, but similar in length to breakthrough therapy approvals at less than five years. However, this expediency also seems to have come with tradeoff of more limited premarket evidence. Most approvals for these gene therapies were based on one small, single-arm, open-label trial using a surrogate marker as the primary efficacy endpoint. Such evidence is even more limited than that of drugs receiving orphan drug or breakthrough therapy designations. Despite the need for postmarketing studies in the absence of robust evidence supporting the approval of these gene therapies, only for three of the five treatments did the FDA require postmarketing studies.

To mitigate the ramifications of such limited evidence on patients and clinicians, the FDA should require both traditional postmarketing studies as well as continued collection of RWD through the establishment of patient registries to follow patients for longer durations after treatment administration and ensure that this data is made publicly available for patients, clinicians, and researchers to learn from. The FDA should also consider awarding approvals to

⁴³ Wallach JD, Egilman AC, Ross JS, Woloshin S, Schwartz LM. Timeliness of Postmarket Studies for New Pharmaceuticals Approved Between 2009 and 2012: a Cross-Sectional Analysis. *J Gen Intern Med*. 2019;34(4):492-495. doi:[10.1007/s11606-018-4779-x](https://doi.org/10.1007/s11606-018-4779-x)

⁴⁴ Puthumana J, Egilman AC, Ramachandran R, Naushad N, Shah N, Ross J. Early experience with the FDA's regulatory review of novel gene therapies. *BMJ Evid Based Med*. Published online October 11, 2021:bmjebm-2021-111720. doi:[10.1136/bmjebm-2021-111720](https://doi.org/10.1136/bmjebm-2021-111720)

gene therapies with limited premarket evidence conditioned on the timely completion of mandatory and well-designed confirmatory trials.

Antibiotics and Antifungals

Legislators are currently considering additional financial incentives^{45,46} for novel antibiotics and antifungals including those that receive the qualified infectious disease product (QIDP) designation from the FDA. In 2019, the Centers for Medicare and Medicaid Services implemented such an incentive in the form of increased new technology add-on payments and the removal of “substantial clinical improvement” criteria for this additional reimbursement.⁴⁷ While the intent of this rule change was to incentivize manufacturers to pursue antimicrobial drug development given the limited product pipeline amid the growing global threat of antimicrobial resistance,⁴⁸ it fails to address the quality of products receiving this incentive. Prior characterization of pivotal clinical trials for FDA-approved antimicrobials (including a small number awarded the QIDP designation) between 2010 and 2015 have shown that most of these trials were noninferiority studies with none evaluating direct patient outcomes as a primary endpoint.⁴⁹

In our recent research examining the evidentiary basis for approval of these QIDP indications, we found that over 20% were approved based on in vitro studies and a majority were tested in non-inferiority pivotal trials,⁵⁰ which allow for intervention drugs to be less effective compared with older, effective antimicrobials by a prespecified margin.⁵¹ Moreover, nearly half of the QIDP indication pivotal trials failed to enroll patients with potential or confirmed resistance. In fact, the FDA only confirmed efficacy against any resistant pathogens for less than a third of these indications based on their pivotal clinical trials. This suggests these financial incentives may be misaligned, rewarding manufacturers of QIDPs with unclear effectiveness against resistant pathogens, despite receiving this special designation intended for this purpose. Instead of awarding costly financial incentives to unproven treatments, the FDA should have

⁴⁵ Davis DK. *DISARM Act of 2021*.; 2021. Accessed November 2, 2021. <https://www.congress.gov/bill/117th-congress/house-bill/4127>

⁴⁶ Bennet MF. *PASTEUR Act of 2021*.; 2021. Accessed November 2, 2021. <https://www.congress.gov/bill/117th-congress/senate-bill/2076/text>

⁴⁷ Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals. Centers for Medicare and Medicaid Services; 2019. <https://www.federalregister.gov/documents/2019/08/16/2019-16762/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the>

⁴⁸ Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2022;0(0). doi:[10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)

⁴⁹ Deak D, Outtersson K, Powers JH, Kesselheim AS. Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration–Approved Antibiotics, 2010–2015. *Ann Intern Med*. 2016;165(5):363. doi:[10.7326/M16-0291](https://doi.org/10.7326/M16-0291)

⁵⁰ Ongoing work

⁵¹ Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. Published online November 2016. <https://www.fda.gov/media/78504/download>

further discretion in granting the QIDP designation and require sponsors of antimicrobial drug candidates to conduct pivotal clinical trials in clinically relevant patient populations including those are typically excluded and that are designed to prove superiority against known, effective alternatives.

Maintaining On-Site Manufacturing Facility Inspection Requirements

Just recently, the FDA announced that it has again halted any non-mission critical inspections in the United States due to the spread of the Omicron variant of COVID-19.⁵² The agency also announced that it would delay moving forward with key surveillance foreign inspections that were scheduled to restart this month. Moreover, compared to 2019, the FDA completed 1,500 fewer inspections in 2020. As a result, less than half of the 2020 inspections ended with an Official Action Indicated determination compared with 2019 inspections. While the agency has pivoted to more remote forms of evaluation of manufacturing facilities, this does not fulfill surveillance inspection requirements of being conducted in-person and on-site. Such inspections are critical to ensuring safe, high quality, and effective medical products for patients. Instead of halting these important checks, the FDA should allocate further resources towards safely continuing these essential in-person, on-site inspections instead of substituting these with remote, paper-based alternatives.

Upholding FDA's Legally Mandated Responsibility to Enforce Reporting of Clinical Trials Results Information

Under the Food and Drug Administration Act of 2007, clinical trial sponsors are mandated to register and then later, submit results information to ClinicalTrials.gov, generally within 12 months of the trial's primary completion date.⁵³ Transparency of such results information is important as it informs clinical care decisions and accelerates future research endeavors. Although sponsors have largely met the requirement to register and submit their trial protocols, reporting of results information remains limited despite this legal mandate and further guidance from the NIH and FDA.^{54,55} As of January 18, 2021, nearly 60% of trials failed to report their results on time and more than 30% (almost 3000 clinical trials with primary completion dates on or after January 18, 2017) had not yet reported results.⁵⁶ The FDA and NIH

⁵² Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. Published online November 2016. <https://www.fda.gov/media/78504/download>

⁵³ National Institutes of Health, Department of Health and Human Services. *PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION*.; 2017. Accessed August 17, 2021. <https://www.ecfr.gov/>

⁵⁴ *Id*

⁵⁵ Food and Drug Administration. Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. Published online August 2020. Accessed August 18, 2021. <https://www.fda.gov/media/113361/download>

⁵⁶ DeVito NJ, Goldacre B. Evaluation of Compliance With Legal Requirements Under the FDA Amendments Act of 2007 for Timely Registration of Clinical Trials, Data Verification, Delayed Reporting, and Trial Document Submission. *JAMA Internal Medicine*. Published online May 24, 2021. doi:[10.1001/jamainternmed.2021.2036](https://doi.org/10.1001/jamainternmed.2021.2036)

share responsibility for enforcing FDAAA although the NIH has historically declined to take any enforcement action on its own, instead waiting for the FDA to do so.

Through an ongoing Freedom of Information Act-based investigation, we obtained all enforcement actions that the FDA has taken regarding FDAAA noncompliance as of late April 2021.⁵⁷ These were all in the form of Preliminary Notices of Noncompliance (or Pre-Notices), of which FDA had issued only 58 in total to trial sponsors; of these, fifty-seven were issued for potential missing clinical trial results information. None of these Pre-Notices were issued to federal agencies, including the NIH despite the NIH being the sponsor for many trials that have failed to submit their results information to ClinicalTrials.gov as required.⁵⁸ We also found that these Pre-Notices were extremely effective at improving compliance – as of mid-August of last year, more than 90% of the recipients had reported missing information to ClinicalTrials.gov within a median time of three weeks.

The FDA has since issued three Notices of Noncompliance to those recipients of Pre-Notices who had still failed to submit their missing trial results information.⁵⁹ With these Notices come the warning of costly, daily civil penalties and possible criminal prosecution should the sponsor fail to act. Upon receiving these Notices, all three sponsors swiftly reported their missing trial results information to ClinicalTrials.gov. It is clear, however, that the FDA could and should send more Pre-Notices and Notices and make these enforcement efforts publicly know, including through ClinicalTrials.gov. Such transparency would improve public accountability and encourage more prompt submission of missing results information. Funding through user fees or through Congressional appropriation should also be directed to support the FDA in their legal enforcement obligations to further improve the submission of clinical trials results information.

Increasing Overall Transparency of Regulatory Decision-making Processes

Within the user fee agreements, the FDA has committed to further increasing their communication efforts with industry throughout the initial review process. They have also proposed various pilot programs (e.g. Split Real Time Application, Rare Disease Endpoint Advancement, Advancing Real World Evidence) and enhancements to established programs around expedited review pathways where the agency plans to work closely with industry partners to more efficiently review candidate drugs and biologic medicines. While the FDA has noted instances where they would host public workshops that would be made available to stakeholders outside of industry, further commitments from the agency to solicit and ensure participation from independent stakeholders are necessary.

⁵⁷ Ramachandran R, Morten CJ, Ross JS. Strengthening the FDA's Enforcement of ClinicalTrials.gov Reporting Requirements. *JAMA*. Published online November 12, 2021. doi:[10.1001/jama.2021.19773](https://doi.org/10.1001/jama.2021.19773)

⁵⁸ FDAAA TrialsTracker. Accessed January 31, 2022. <http://fdaaa.trialstracker.net/>

⁵⁹ Food and Drug Administration. ClinicalTrials.gov - Notices of Noncompliance and Civil Money Penalty Actions. FDA.gov. Published September 1, 2021. Accessed October 8, 2021. <https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions>

In the case of aducanumab, the FDA was reported to have engaged in an unusually close collaboration with the manufacturer, Biogen during the regulatory review process.⁶⁰ Despite FDA's own independent advisory committee nearly unanimously voting to not approve this drug,⁶¹ the agency proceeded to continue to work with Biogen behind closed doors on its application. This led to the controversial decision to approve the drug through the accelerated approval pathway based on an unproven surrogate marker.⁶² Just months before, FDA officials had assured the advisory committee that they would not be using this biomarker "as a surrogate for efficacy."⁶³ Learning from this experience, the FDA should institute a firewall between staff engaged in assisting manufacturers in their submission and those that conduct the review. By doing so, patients and clinicians will be more assured that the agency is maintaining its own independence without undue influence from drug sponsors in making regulatory decisions.

When the FDA does adopt a more transparent approach, it has had success in instilling public trust in its regulatory decision-making process. With COVID-19 vaccines and therapeutics, the FDA has hosted an unprecedented number of public advisory committee meetings where anyone can view discussions between this group of independent experts and FDA officials.⁶⁴ Moreover, the FDA has made available review summaries for COVID-19 vaccines and drugs ahead of these meetings and upon emergency use authorization despite there not being a statutory mandate to do so as with approvals.⁶⁵ This has allowed other independent experts, clinicians, and patients to review the submitted evidence themselves and better understand the FDA's rationale in making regulatory decisions. As a minimum, the FDA should employ such practices when making regulatory decisions for other disease areas.

Adopting more transparent approaches to instill public trust in FDA's decision-making process should not be "one-size-fits-all", but rather adapted to the complexity of the regulatory decision and public health need. Although the FDA did convene an advisory committee for aducanumab in November 2020, the drug's approval became predicated on a separate review pathway that was never discussed with this group of independent experts.⁶⁶ Thus, when the FDA decided to approve aducanumab, this surprised its own advisory committee, prompting the

⁶⁰ Feuerstein A, Herper M, Garde D. Inside "Project Onyx": How Biogen used an FDA back channel to win approval of its polarizing Alzheimer's drug. *STAT News*. Published June 29, 2021. Accessed January 31, 2022. <https://www.statnews.com/2021/06/29/biogen-fda-alzheimers-drug-approval-aduhelm-project-onyx/>

⁶¹ Food and Drug Administration. Peripheral and Center Nervous System Drugs Advisory Committee Meeting. Published online November 6, 2020. Accessed January 29, 2022. <https://www.fda.gov/media/145691/download>

⁶² Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid- β -targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019;15(2):73-88. doi:10.1038/s41582-018-0116-6

⁶³ Food and Drug Administration. Peripheral and Center Nervous System Drugs Advisory Committee Meeting.

⁶⁴ Gupta R, Schwartz JL, Ross JS, Kanter G. During COVID-19, FDA's Vaccine Advisory Committee Has Worked To Boost Public Trust – It Can Still Do More. *Health Affairs Blog*. Published February 26, 2021. Accessed January 26, 2022. <https://www.healthaffairs.org/doi/10.1377/forefront.20210225.712221/full/>

⁶⁵ Food and Drug Administration. Emergency Use Authorization. FDA. Published January 31, 2022. Accessed January 31, 2022. <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>

⁶⁶ Alexander GC, Knopman DS, Emerson SS, et al. Revisiting FDA Approval of Aducanumab. *New England Journal of Medicine*. 2021;385(9):769-771. doi:10.1056/NEJMp2110468

subsequent resignation of three members.⁶⁷ Instead, the FDA could have convened the advisory committee once again to discuss the possibility of this alternative pathway for approval and maintained continued communication with members throughout the approval process.

Finally, further transparency and reforms are needed in FDA's process for engagement of stakeholders in shaping user fee agreements. Currently, the FDA convenes industry stakeholders separately from other public stakeholders for their discussions on what should be included within user fee agreements.⁶⁸ While the FDA posts summaries of these meetings online, these are quite brief with little to no detail on what specific proposals were discussed nor the considerations posed by the stakeholders who participated. As these discussions around user fee agreements are not specific to individual drugs or biologic medicines, it is unclear why this separation in FDA's interactions with industry and public stakeholders exists or why such information would need to be kept confidential. Should truly commercially confidential information need to be considered as part of these negotiations, the FDA could convene relevant stakeholders separately for that purpose.

In reviewing the PDUFA VII Commitment Letter put forward by the FDA in late September of last year and recently released draft legislation, the provisions seem to be almost identical despite public comments from independent patient and consumer advocacy organizations calling for specific revisions to the proposed agreement. The FDA in their response to these public comments stated that they have "not made changes to those recommendations for the reauthorization of PDUFA" with the rationale that there is "general support for the PDUFA VII agreement."⁶⁹ Coupled with the FDA's current policy of having separate, non-transparent negotiations with biopharmaceutical companies and trade associations, the agency has seemingly put more weight on industry recommendations rather than those organizations who independently represent the public's interest. Convening all stakeholders together for future user fee agreement negotiations would be a first step towards restoring balance to an asymmetry of influence on FDA's process in drafting its user fee commitment letters and legislation.

As clinicians, we often have discussions with our patients about potential treatment options. In those discussions, we consider both the potential benefits as well as the potential risks in making specific clinical care recommendations. Ultimately, we work in partnership with our patients in developing a treatment plan that centers their health and well-being above all else and where the benefits outweigh the risks as much as possible. With these user fee agreements, Congress and the FDA must take a similar approach, considering both the benefits and the risks, both short-

⁶⁷ Mahase E. Three FDA advisory panel members resign over approval of Alzheimer's drug. *BMJ*. 2021;373:n1503. doi:[10.1136/bmj.n1503](https://doi.org/10.1136/bmj.n1503)

⁶⁸ Food and Drug Administration. PDUFA VII: Fiscal Years 2023 – 2027. *FDA*. Published August 23, 2021. Accessed January 31, 2022. <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027>

⁶⁹ Food and Drug Administration. Summary of views and comments received to Docket No. FDA-2021-N-0891 regarding proposed recommendations for PDUFA VII. Accessed January 31, 2022. <https://www.fda.gov/media/155023/download>

and long-term, of the included proposals. It is clear to me that overall, the benefits of having an adequately funded FDA outweigh any potential risks. However, further reforms must be made to ensure that the FDA is fulfilling its mandate and promise of protecting and improving our patients' and our nation's health.

Ms. ESHOO. Thank you.

We now will move to member questions, and I recognize myself for 5 minutes to do so.

Right back to you, Doctor. In what you just presented to us in the accelerated trials, can you give us examples of outcomes that hurt patients?

And was this raised, what you just testified to? Did you raise this during the negotiations?

Dr. RAMACHANDRAN. I thank you so much, Congresswoman, for the question.

So just some relevant examples, particularly with cancer drugs that have been approved through this pathway, we have found that a number of the trials use the same surrogate endpoint in the post-approval trials as the pre-approval.

Ms. ESHOO. Wait a minute. Slow down a little bit so I catch every word.

Dr. RAMACHANDRAN. Sure.

Ms. ESHOO. Say that again.

Dr. RAMACHANDRAN. Sure. We found for cancer drugs that were approved through the accelerated approval pathway, their confirmatory trials used the same surrogate endpoints in their confirmatory trials, which are meant to show clinical benefit, as the pre-approval trials.

So the clinical endpoints that were surrogate endpoints did not correlate or were not associated in many cases with clinical and meaningful outcomes, such as, you know, patient survival, whether there was mortality and morbidity, patient function.

And so those we see as harms in the sense that accelerated approval is this idea that we should be able to confirm whether or not these drugs are truly clinically beneficial after they are approved and also to make sure that patients, when they are taking these drugs know for a fact that when they make these financial decisions to be able to take these drugs, that they know for certain that it is actually clinically effective and safe.

A number of my colleagues, including physicians and others, did raise this in the PDUFA meetings, but they wanted to make sure that the accelerated approval pathway did mandate that confirmatory trials—

Ms. ESHOO. Well, let's just get to another point. In terms of this discussion in the negotiations, what is changing?

Dr. RAMACHANDRAN. And so right now at least in response to the public stakeholder comments, when we put forward these different types of metrics that we wanted the FDA to look at, they are more patient centered.

Unfortunately, the FDA responded that they would not be making these changes. So that has not been included into the negotiations.

Ms. ESHOO. OK. Let me go to Ms. Reed.

I think that we have known each other for a long time, and I am proud to have been the House sponsor of the Pathway for Biosimilars Act in 2008. It was folded into the ACA, and it was first granted the FDA or, you know, it was a first, a first.

Today the biosimilar market is expanding. I have to say that I have been frustrated along the way even though it is said that it

is set to double in size by the year 2025, except I do not think the market has really taken off since Congress put the legislation into law.

Can you just give us a brief profile of what is to come out of biosimilars?

I know that the FDA did testify this morning as to how many have been approved, and that is encouraging. Do you have more to add to that?

Ms. REED. Thank you, Chairwoman, and thank you. This has been a wonderful adventure for me to partner with you on this commitment.

Yes, I can definitely do that, and I think, first of all, to the agency's commitment and our commitment to the agency's program is significant, and that is a very good thing, and that is why we support the BsUFA III.

But as you know and said, more can be done for the uptake and the access of biosimilars, and that is something the Forum is committed to.

We need to change the way biosimilars are incentivized for it to get to patients. Biosimilars are a cost saving solution on the shelf ready to go. If we were to see that patients had access to 90 percent of the time to a biosimilar, this country will save the billions of dollars that we predict will be available and have an incredible cost savings for consumers, patients, and the government.

There are a number of ways we can do that. We can incentivize. We can continue to combat missed information. We can look at—

Ms. ESHOO. My time is running out.

Ms. REED. Thank you.

Ms. ESHOO. Did you raise all of this during negotiations?

And if so, what is the—

Ms. REED. Yes.

Ms. ESHOO. Are any of these things that you are raising being addressed?

Ms. REED. Thank you, Congresswoman and Chairwoman.

These things need to be addressed outside the user fee programs. So we have a commitment to accelerate and streamline development of biosimilars with the agency, but we would love the opportunity to work with you and the committee and look at—

Ms. ESHOO. My time is—I do not want to set a bad example for my colleagues. My time has expired, but we can continue this conversation with follow-up written questions to our witnesses.

It is a pleasure to yield to our distinguished ranking member of the subcommittee, Congressman Guthrie.

Mr. GUTHRIE. Thank you. Thank you, Madam Chair.

You know, some of the biggest influencers on Capitol Hill are families and people who have diseases. They come to see our offices. I think, as the Chair would say, we have quite a few people that visit it and make a big impact because they tell their stories and they tell their lives.

And so what we try to do and what we try to push in public policy is to get these miracle cures, if they are miracle cures, and drugs and pharmaceuticals to the patient as quickly as possible, accelerated if possible, but it also needs to be safe and effective.

And so that is where we try to balance what we do and have a lot of faith in what the FDA does moving forward, but I do not know. I know you have every year this. We had a hearing where they all left. I think that had a big impact on a bill that moved forward with the patient that came here from Chicago.

And so, Dr. Esham, you know, I voiced my concerns with CMS early on their Aduhelm, the way they had limited circumstances offering in addition to the process they took.

Could you use that as an example of how or do you believe that this decision will impact future investments in these potential life-saving drugs?

And just talk about what are the issues that you take with that process CMS went forward with.

Dr. ESHAM. Certainly. I would say that the decision it finalized will have a chilling effect not just on the future of investment in the research and development for innovative Alzheimer's treatments, but for other treatments to treat difficult disease.

As you know, producing a novel therapeutic is one of the riskiest business ventures an entrepreneur can take, and importantly, most of the science and research being conducting today has been conducted by small companies that are reliant on venture capital.

And those significant investments that are necessary to advance this work are predicated in large part on a stable and understood pathway from approval to access, where FDA makes determinations on safety and effectiveness, and CMS makes a determination of reasonable and necessary, where coverage is provided for treatments to be used as indicated on FDA-approved labels.

Further, the assertions to and impact on an entire class of drugs as proposed under this NCD proposal are really untenable from an investment standpoint.

Mr. GUTHRIE. OK. Thank you.

And Dr. Vereshchagina—I am sorry—some work on legislation. So here is another thing that we have. We have, I think, what Dr. Ramachandran talked about.

You know, it is not just investment that goes in from the company putting forward. Once it comes out, it is the investment that the individual and the patient puts into buying the pharmaceutical either through their health insurance or out of their pocket or however they move forward.

And so we want to make sure that they are available, and some of these can be expensive because a lot of research goes into it.

And so I have worked with Congressman Schrader. The information—well, that was not with him. I am sorry—the Information Exchange Act of 2017, and what that is it allows during the Phase 3 trials for there to be discussion between payers and pharmaceutical companies to determine what, because the idea would be if there is a breakthrough drug that comes out on day one, day two they can make a coverage determination, and obviously a payer has to have the financial information to know how to put it in their formulary, and so forth.

You know, there has been some resistance here to say, well, that is marketing a drug before it has been approved, but the thing is then you wait a year, and understand the issues that are raised with that.

And I think we can deal with it and make sure we have a pharmaceutical. You hear migraine. They come out quite often, and I know people with migraines. "I do not think I can get this drug." And it takes them a while to get a coverage determination.

Could you talk to how if we could have discussions particularly in Phase 3 where we know there has to be some success with the drug or it would not be in Phase 3 and with payers and how that would benefit the marketplace?

Dr. ESHAM. Certainly. So you mentioned the Pharmaceutical Information Exchange Act in 2017. So my understanding is FDA issued the final guidance to help implement provisions in this act, and from what we hear, the guidance helped to facilitate productive communications between FDA, sponsors, and payers.

So while we cannot comment on any specific proposal, PhRMA will welcome an opportunity to work with you and your office to make sure that any further legislative proposals accurately reflect the final guidance, and they really help to facilitate those productive discussions and conversations with payers.

Mr. GUTHRIE. What if we just codified the final guidance so there is not a new proposal? Just the final guidance comes and we codify it.

Because the problem you hear is not just in pharmaceutical, but in almost every deal that we deal with, is people say, "Well, we do not know." The uncertainty of the regulatory environment and things that Congress can put into law makes certainty better.

And so that is my question, if we codified the guidance that came out.

Dr. ESHAM. So I am not a lawyer. I would definitely defer to a lawyers and legislative experts whether codifying the guidance would make a meaningful impact.

But PhRMA does agree that the final guidance was helpful in promoting such productive communications with payers.

Mr. GUTHRIE. OK. What we hope to do is have, if drugs are going to make a big impact on people's lives, approved as soon as possible they are safe and effective and approved as soon as possible by payers to make sure that people have access to these cures.

And as I said, and I will close with this. I have gotten to know families and I have seen families. I have been to funerals of families who have been here and talked to us and advocated, and people are in desperate situations, and the American pharmaceutical industry addresses it, but it also is expensive, and we have to have a way to pay for it and make sure people have access to it.

We appreciate the investment, and we certainly appreciate the cures. But we want to make sure we get coverage.

So thank you, and I yield back.

Ms. ESHOO. The gentleman yields back.

It is a pleasure to recognize my colleague from California, the gentlewoman from California, Congresswoman Matsui, for your 5 minutes of questions.

Ms. MATSUI. Thank you, Madam Chair.

And I want to thank our second panel of witnesses for being here today.

I want to follow up on some discussion on biosimilars. The biosimilars competition is key to lower drug prices, and I am concerned that existing inspection backlog will stifle opportunities.

Now, we heard today how the pandemic has disproportionately impacted inspections and review timelines for biosimilars in comparison to the other user fee programs.

Additionally, with more than 30 approved biosimilar products today, industry is expected to submit more supplemental applications to FDA over the next five years.

Ms. Reed, the third biosimilar agreement includes new pre-market review processes for certain applications. Can you expand on how these processes will accommodate incoming supplements from sponsors, and why this is important to advancing a robust biosimilars program?

Ms. Reed?

Ms. REED. Thank you, Congresswoman, for that question.

So these enhancements, especially in the BsUFA III, are very important because they reflect the evolution of the science and technology for biologics and biosimilars.

So those enhancements will shorten the time frame for responses and communications between sponsors, as well as the agency; require less data from sponsors, which is very important because the streamline will lower the cost.

Ms. MATSUI. OK. Good. Is it Dr. Gaugh? Is that how you pronounce your name, Gaugh?

Mr. GOUGH. Yes.

Ms. MATSUI. In your testimony, you discuss the challenges of developing complex generics. As we heard from the first panel, the BsUFA III agreement includes a new midcycle review meeting commitment between industry and regulators for a complex generic drug application.

In your view, what information can industry learn from these new opportunities that were missing in the current review cycle practice?

Mr. GOUGH. Thank you for the question.

Yes, so in GDUFA II we started building a complex generic structure that would allow and would somewhat mimic the new drug development process, and by that I mean allowing the companies to have a pre-development meeting with the FDA, a pre-filing meeting with the FDA, a midcycle meeting, and then an end meeting with them.

We were not able to gain all of those accesses in GDUFA II, and we also asked for the product-specific guidances to be enhanced in GDUFA II, which, again, that was not able to happen.

In GDUFA III, however, we have continued down that path. So we now have those pre-development meeting capabilities that we can ask for with the FDA. They do not necessarily have to grant them, but we can ask and hopefully will get those.

We also have the midcycle review meetings, and then we have the more robust product specific guidance structure setup.

Thank you.

Ms. MATSUI. Thank you.

Now, I would like to follow up on the discussion we had with the FDA earlier. There was a lot of work to advance the development

of therapies and cures for rare diseases. Because drug development for rare diseases typically focuses on novel areas that affect few patients, the critical trial populations are often inherently small, and there is a lack of regulatory precedence for drug development.

Dr. Esham, from your perspective, how would a rare disease endpoint advancement pilot program help industry better design clinical trials for rare disease and treatments?

And how would that impact the rare disease drug development process overall?

Dr. ESHAM. Thank you for that question.

I just want to make sure. Are you questioning about the provision in the PDUFA agreement about the rare disease endpoint pilot, correct?

Ms. MATSUI. Right, right.

Dr. ESHAM. We do think it will be highly valuable, as Dr. Marks said in his earlier testimony. The ability to have stronger engagements that will allow for scientific dialogue about how best to approach the development, solve and support for utilization of an endpoint in rare diseases, which does have its own unique challenges, will be highly beneficial.

And it is beneficial these kinds of pilots are built to be beneficial beyond, not only those that are in the pilot program, but it is set up to ensure that the learning and best practices are shared to the entire research and development community.

So we really do think that this pilot program offers true value and will be broadly applicable to help researchers understand what needs to be done to develop and support utilization of endpoints for rare diseases.

Ms. MATSUI. So you believe that the lessons learned from this pilot program and other initiatives for rare diseases throughout the review process can help the review program practice for other programs?

Dr. ESHAM. Yes, absolutely. The key provisions in those user fee agreements are the ability for the FDA to share information from the applications that were part of the pilot program so that they can share them more broadly with the entire research and development community. That is right.

Ms. ESHOO. The gentlewoman's time has expired.

The Chair is pleased to recognize the gentleman from Georgia, Mr. Carter, for your 5 minutes of questions.

Mr. CARTER. Thank you, Madam Chair.

And thank you all for being here.

Very quickly, as a pharmacist, drug shortages are extremely important, and for me personally, and it is something that I have been working very diligently on and I continue to.

Also moving pharmaceutical manufacturing back to America, that is one thing. You know, I often say there is a difference in knowing something and realizing something. We knew we were too dependent on other countries for our pharmaceutical needs pre-pandemic. We realized it during the pandemic.

We have to do this, and I have got legislation that will do just that, but one of the things is innovative manufacturing technologies. This could help. It could help solve the drug shortage

problem as well as to help incentivize pharmaceutical manufacturers to move their production back here to America.

But it seems the FDA review process for these technologies is slowing this innovative manufacturing, and I just wanted to ask you Dr. V. I ask you first. Can you speak to the importance of approving innovative advanced manufacturing technologies and their benefit for manufacturers and, most importantly, for patients?

Dr. VERESHCHAGINA. Absolutely. So industry and FDA recognize that it is a critical issue, and this is why PDUFA VII, actually the first time in the history of user fees, includes manufacturing provisions, and advanced manufacturing Section 08 [inaudible] manufacturing and risk-based inspections are all included in PDUFA VII.

So we do hope that it will help expedite all the things that you just mentioned.

Mr. CARTER. OK. Well, I am going to hold you to that, and I hope it does because we need this. This is essential.

And, Dr. Esham, do you want to add to that? Is there anything you can add to it?

Dr. ESHAM. No, I will underscore that we believe the ability of these technologies due to the promises that they offer, optimization of efficiency, scalability, reducing variability, and increasing product quality assurances, all of which are good for patients in ensuring expedited availability of high-quality medicines.

Mr. CARTER. Good. Thank you both for that.

Mr. Gough, I want to ask you. One of the things in my many years of practice in pharmacy, I often say that I have seen nothing short of miracles through research and development, and I have not.

I use the example quite often, and I think it is a good example of Hepatitis C. I remember when I started practicing pharmacy back in 1980, that if you were diagnosed with Hepatitis C, you were going to die. I mean, we did not have anything to treat it.

Now we can cure it with a pill. That is phenomenal, but if you cannot afford that pill, it does you no good whatsoever.

That is something that is extremely concerning to me. I know that GDUFA III is supposed to improve FDA's review and approval of complex generics because generic drugs, and it baffles me and frustrates me to no end that it takes so long for a generic to get to the market.

I always thought that, quite honestly, before I became familiar with the process, I always thought working as a pharmacist that, OK, they get seven years and then on day seven year and one, then the generic comes out.

But I have learned since I became a member of Congress and a member of this committee particularly that is not the case at all. It may be years and years after that.

GDUFA III, is that going to improve that at all?

Mr. GOUGH. Yes, we believe it is going to improve. So a couple of things.

One, I talked a minute ago about the complex generic pieces that we have built into GDUFA III which will help move that along.

The second thing is first cycle approvals instead of, to your point, several years. We have a ten-month goal in the approval process, but what we found was that at the end or not the end, but at nine-

ish months that review cycle may not be close enough or close but just not there yet to get an approval. And so we get a complete response letter instead of approval.

So we built in an imminent approval piece that adds an additional 60 days to that to allow the FDA and the company to work together to meet that deadline.

Mr. CARTER. Is there any way we can get that process started earlier?

They know in seven years the patent is expiring. Can they not get it started like two years before then or in year five or whatever?

Mr. GOUGH. Well, in many cases we do. We file—

Mr. CARTER. And it still takes that long to get a generic to market?

Mr. GOUGH. Depending on the product and the product category, yes. But many products are tentatively approved by the FDA, and to your point, ready to launch the day after the expire date or the day of the expire date.

Mr. CARTER. I think we see that happen seldom. I think it is the other way around. I think it is years later more often than it is the day after.

Mr. GOUGH. It can be, but it is both actually.

Mr. CARTER. Well, is there anything we can do in Congress to accelerate that?

Mr. GOUGH. Approve this User Fee Act and that will help a lot, yes.

Mr. CARTER. OK. Thank you all.

Mr. GOUGH. Thank you.

Ms. ESHOO. The gentleman's time has expired.

The Chair now recognizes the gentleman from Maryland, Mr. Sarbanes, for your 5 minutes of questions.

And I would also like to add that I have one other from our side that is waiting to question, and that will be it, and then—09

Mr. GUTHRIE. We are letting our people know.

Ms. ESHOO. Good. OK. So, Mr. Sarbanes, you are on.

Mr. SARBANES. Yes, thank you. Thank you much, Madam Chair. And I want to thank the panel.

We certainly know that R&D investments of pharmaceutical companies are absolutely critical to advancing new therapies, but too often, I think, industry claims that we must make a false tradeoff between promoting innovation, on the one hand, and the affordability of increasingly expensive prescription drugs millions of Americans rely on, on the other hand.

Dr. Ramachandran, can you speak to whether this tradeoff really exists and the role that legislation being discussed in Congress, including the GDUFA proposal before us today, can play in impacting the affordability of prescription drugs?

Dr. RAMACHANDRAN. Thank you, Congressman, for your question.

This tradeoff does not really exist that we are seeing, and unfortunately, our patients are the ones that are hearing things, kind of the bad end of a bad bargain from that tradeoff.

Just to kind of reiterate one of the points that has been made earlier, you know, in relation to Aducanumab, the drug that was recently approved by the FDA based on a surrogate endpoint that

two dozen clinical trials found no association with a clinically meaningful outcome for patient, you know, a number of people had concerns about this. They had three resignations that came through after that approval went through by the FDA.

And it has actually sent a signal of bad innovation to the industry instead of, you know, truly incentivizing innovation that is going to be clinically meaningful to patients.

Instead a number of other manufacturers came in to want to make similar drugs with the same mechanism of action that is unproven, and so who is going to lose in that situation? Our patients. Our patients are going to be flooded with, you know, a number of drugs that are not going to be very good or beneficial for them both medically and financially.

The GDUFA agreement and BsUFA agreement, I am grateful for the fact that there are mechanisms within that to make the process more efficient for biosimilars and generics to be produced, to be, you know, reviewed much more quickly, and also to get out to patients because I have seen the impact of those generic and biosimilars on my own patients, particularly generics.

You know, a number of my patients, especially my older adult patients who take multiple medications, have significant cost savings as a result of the availability of generics and biosimilars.

Woodcock had sent a letter to the Patent Office last year and had talked to them specifically about collaboration through additional barriers that are impeding biosimilar access and generic access, in particular.

And I am hoping that these agreements will actually include metrics on FDA's collaboration with the PTO or there might be legislation to kind of ask about this a little bit further to see if those questions that are being asked to the PTO are going to be realized through regulatory action.

Thank you.

Mr. SARBANES. Thank you.

Let me ask you a little bit about the source of dollars to support these reviews. It is certainly clear that you are going to need adequate resources to take on the wide [audio malfunction] work of keeping Americans safe.

I have some concerns that a large portion of FDA's budget is attributable to user fees from the industries that are being regulated. For example, in fiscal year 2020, FDA spent about \$400 million from congressional appropriations on the PDUFA program compared to almost \$1.1 billion from user fees.

[Audio malfunction] have confidence in scientists and other [audio malfunction] at the FDA, but, Dr. Ramachandran, in your testimony you described some of the challenges the FDA faces in the public trust given its close ties to the industry.

Can you briefly outline some of the points that you raise on this topic?

Dr. RAMACHANDRAN. Thank you, Congressman, for that question.

You know, like a number of my colleagues, especially my other fellow physicians and patients, we do have concerns that FDA's increasing reliance on industry user fees has led to faster approvals, but also faster approvals where we have more uncertainty on clinical benefit and safety.

So you know, short of not having enough congressional appropriated funding to ensure the independence of the FDA, I am hoping the user fee agreements will include a number of provisions that are safeguards to protect patients and to instill that public trust.

And one of those that I have mentioned in my testimony, both written and today, was around these metrics that are more patient centered and not just on industry benchmarks.

Thank you.

Mr. SARBANES. Thank you very much.

I yield back.

Ms. ESHOO. The gentleman yields back.

The Chair now recognizes the ranking member of the full committee, Representative McMorris Rodgers, for your 5 minutes of questions.

Mrs. MCMORRIS RODGERS. Thank you. Thank you, Madam Chair.

I had a couple of questions for Dr. Vereshchagina and Dr. Esham.

When we discuss the importance of including diverse populations in clinical trials, we cannot forget those with disabilities, especially those with developmental disabilities. How can we improve representation of those with disabilities in the clinical trials?

Dr. VERESHCHAGINA. I can start and, Dr. Esham, I will pass to you.

This is why we are excited about digital health technology provisions in PDUFA VII, which are intended to enable what we call remote or decentralized clinical trials.

And in such trials, it is possible to collect data remotely. As we heard this morning perhaps patients do not have to travel to clinical trial sites that are far from their home. They can see a doctor hopefully in their community.

Maybe some data can be collected through wearables. So we believe digital health technologies have great potential for the future of clinical trials.

Mrs. MCMORRIS RODGERS. Yes, I agree.

Dr. ESHAM. And I concur with my colleague and her statements.

I will add a few additional thoughts, and that is we concur that inclusivity needs to be all-encompassing. We at BIO have developed a detailed proposal outlining key steps and activities for the FDA and cross-agency activities we think will enable a more inclusive clinical development ecosystem.

And among those are discussions relating to inclusion and exclusion criteria, which under current practices may be prohibiting participation from specific segments of the patient community, including those with disability.

So we would be happy to share with you and discuss in more detail if you would find that beneficial.

Mrs. MCMORRIS RODGERS. Yes. I am quite dismayed by the recent coverage determination by CMS with respect to the coverage for all FDA approved drugs targeting Amyloid for the treatment of Alzheimer's. It appears to be entirely excluding Americans with Down's Syndrome from any form of coverage while trials are ongoing to meet the coverage with evidence development requirements.

I am very concerned about the precedent that this is setting. Could the exclusion of individuals with Down's Syndrome from the CMS-covered trials disincentivize the recruitment of clinical trial participants from this population in the future study for drugs targeting Amyloid?

Yes. I was going to ask the two of you again.

Dr. ESHAM. Do you want me to go first this time?

Mrs. MCMORRIS RODGERS. Or if others want to speak to it.

Dr. ESHAM. Well, as I stated earlier, we have many concerns about the proposed national coverage determination. Not only could it negatively impact the future of AZ research, but the uncertainty it creates for all future approvals of innovative medicines.

It is imperative that the mandates and distinct mandates of CMS and FDA are maintained.

But more directly to your question, the provisions, the additional provisions in the coverage that may, in fact, compound or delay medicines for patients with disabilities is equally troubling.

Mrs. MCMORRIS RODGERS. And have you ever seen this before?

Dr. ESHAM. I believe "unprecedented" is a term that leaps to mind.

Mrs. MCMORRIS RODGERS. OK.

Dr. VERESHCHAGINA. And I would echo what Dr. Esham just said. PhRMA is concerned about the proposal and especially about potential negative impacts that it may have on access for patients, especially since it affects a broad class of drugs, including some of those that are still in development that have not even been approved yet.

Mrs. MCMORRIS RODGERS. Yes. Does anyone else care to speak to this question?

Dr. RAMACHANDRAN. Yes, I can definitely speak to this.

Mrs. MCMORRIS RODGERS. That would be great.

Dr. RAMACHANDRAN. The national coverage determination is not as unprecedented as one might think. There has been other coverage with evidence development determinations where they have required a greater amount of controlled trials, and I am happy to share that information with the Congresswoman, you know, after the hearing.

The one thing I will say is that as a physician and someone who has reviewed the clinical trial evidence from Aducanumab where that surrogate endpoint that you have mentioned, there has not been an association with a clinical meaningful outcome.

So I am grateful that the CMS is actually allowing for further evidence to be generated so that patients are not paying \$28,000 per year for a drug that might not work and that might cause harmful side effects, such as brain swelling and brain bleeds.

Mrs. MCMORRIS RODGERS. Why was that not raised with FDA?

Dr. RAMACHANDRAN. It was raised with the FDA. The Advisory Committee, and this is actually a quote from the FDA official, that they were not going to consider Amyloid as a surrogate endpoint. They did not feel that it was sufficient to actually determine efficacy.

But then later after conversations with the manufacturer, which was found in multiple reports, and when they did not reconvene

the Advisory Committee, they went ahead with the accelerated approval.

Mrs. MCMORRIS RODGERS. Have you ever seen a class of drugs limited for people with disabilities?

Dr. RAMACHANDRAN. So in the number of clinical trials the way that enrollment works what a number of manufacturers do unfortunately is that they exclude oftentimes sick patients in which they are concerned that they will not see a positive benefit from the drug.

So I am grateful that the FDA and the Congresswoman are paying attention to the fact that these trials' enrollments need to be adjusted to also include patients with other comorbidities, including developmental disabilities.

Mrs. MCMORRIS RODGERS. OK. Thank you.

I will yield back.

Ms. ESHOO. The gentlewoman yields back. And we all appreciate your staying on this issue of the disabled, and I do not think really very much is going to change unless and until we have real diversification in clinical trials. That is a must, and many of us have legislation drafted and have offered it on that.

We really should come together and make up our minds and get a really solid bill through.

Now, we have Mr. Cárdenas, the gentleman from California who is next, followed by Mr. Curtis, and I do not have any others, but votes are going to be called pretty soon. So we want to conclude.

So, Mr. Cárdenas, you are recognized for your 5 minutes of questions.

Mr. CÁRDENAS. Thank you very much, Madam Chairwoman and Ranking Member, for this opportunity for us to have these amazing panels to help educate not only ourselves but the public on what we are doing here in Congress to make sure that we can still have the best process in the world when it comes to approving safe solutions to people's health. So thank you so much.

And also to the witnesses, I appreciate your expertise and your thoughtfulness and your insightfulness in being with us today.

Dr. Ramachandran, thank you for being here, and thank you for the critical work that you do.

I am especially interested in your recommendation for more patient-centered performance measures when reviewing applications. Obviously, the most critical aim of the review process is to ensure that any approved therapies are safe and effective.

Why are patient-centered metrics important to include?

And how do we best balance a patient-centered perspective while maintaining a reasonable timeliness?

If you can be brief because I have another question for you.

Dr. RAMACHANDRAN. Yes. Thank you, Congressman, for the question.

You know, patient-centered metrics, the way that I view them is that it will help actually incentivize truly clinically meaningful innovation. FDA sets regulatory standards, and it oftentimes becomes the bar by which other companies follow in terms of how they develop new drugs.

So the hope is that including patient-centered metrics where we know for certain how often these approvals are actually clinically

beneficial and safe, how often they are actually requiring post-marketing trials for accelerated approvals that show clinical benefit. All of those will lead to manufacturers being incentivized to do better innovation that truly matters to our patients.

Mr. CÁRDENAS. Thank you.

And based on your experience as a practicing clinician, how have some of your patients benefitted from increased access to safe and effective, yet lower cost generics and biosimilars?

Dr. RAMACHANDRAN. This has just been paramount for my patients. I will tell you I see a number of patients who take multiple medications for multiple chronic conditions, and the things that they have to take for the rest of their lives. And when they are not able to access those medicines, they oftentimes will end up in the hospital or are much more sick. It has been devastating to watch.

When generics have been available for a number of medications, a lot of combination medications, for instance, for heart disease, for high blood pressure, cholesterol and whatnot, these have been incredibly beneficial for my patients because that means that they do not have to make a decision of food and access to drugs or they do not have to make a decision of, you know, having to abandon the medicines at the pharmacy counter and facing some downstream consequences.

So the availability of generics and biosimilars has just been paramount for them to be able to continue to live healthy lives, and it gives me full reassurance that when I prescribe medicine, they are able to access them.

Mr. CÁRDENAS. OK. Thank you so much for that insight.

I would like to continue this focus on biosimilars and some of the promise they show in expanding access to affordable drugs. Biosimilars have proven remarkably effective at driving prices down by introducing lower cost competition in the biologic drug market.

This is especially critical for low-income folks with health conditions who often have to make impossible decisions between affording their medications and putting food on the table.

Today over 30 biosimilars have been approved by the FDA, with many more still in the review process. I want to see the FDA continue its trajectory of increasing approvals for safe and effective lower cost biosimilar drugs, as well as interchangeable biosimilars.

So my question to Ms. Reed, thank you for your work in this area. Based on your testimony, it is clear that you have extensive experience in spreading awareness of what biosimilars can do and how to expand access to them.

What does the evidence say about their effectiveness and what are some of the conditions that they are used for?

Ms. REED. Thank you so much, Congressman, and thank you for your ongoing championship championing the biosimilars and lower cost medicine.

So we have 33 biosimilars approved. And we have a number of other biosimilars approved around the world. We have seen that they are as safe and efficacious and provide the same clinical results of their referenced biologics. So that is very key.

And we continue with the agency with this BsUFA III commitment letter to see that we are advancing the technologies and the commitments and streamlining the development of biosimilars.

What is really key for us though, and this is key if we talk about innovative medicines and access to innovative medicines. We need the funds to provide, to be able to get the access to those.

So biosimilars, lower cost biosimilars are key.

Biosimilars need to be a priority at the agency, and we would like to see that.

Mr. CÁRDENAS. Thank you.

And, Madam Chairwoman, I would be remiss if I did not mention how amazing it is to see so many awesome women testifying today and people from all over the country that look like America with names that are hard to pronounce, but thank you all for all of your amazing, amazing work.

Thank you very much, Madam Chairwoman. I yield back.

Ms. ESHOO. Well, thank you for that wonderful observation. Typical of California thinking as well.

It is a pleasure to recognize the gentleman from Utah, Mr. Curtis, for his 5 minutes of questions, and it looks like you will be the last questioner, and we can wrap up.

Mr. CURTIS. Madam Chairman, it seems like you and I share a theme that just as you want to go vote, it is my turn to ask question.

[Laughter.]

Ms. ESHOO. I know.

Mr. CURTIS. So I appreciate a few minutes and our witnesses this morning.

You know, this morning I mentioned that I am in a unique situation. I have not been on the committee as we have done this process before, and I do not have a healthcare background.

But I also believe that lets me see a little bit of the forest and the trees in the forest from a distance and a different perspective and bringing kind of a problem solving, businessman mentality to this as well.

This morning I also shared a story about a Utahan, a woman who has a son. He is five years old, and he has classic Galactosemia, and this mother is desperate for access to AT007, a central nervous system penetrant inhibitor used to treat this disease.

This drug can change her son's educational trajectory at a time when his mind is developing very quickly and a unique period in his life, what will make a difference to help him be a self-sufficient adult.

I know that this panel may not be able to speak to the specific drug, but I have heard multiple stories about Americans and Utahans like this that I referenced this morning and who are desperate for access to these innovative therapies.

Dr. Vereshchagina and Dr. Gaugh or Mr. Gaugh, how would these agreements being considered before us today help accelerate the approval process for these medical products and give these people hope?

Doctor, we will start with you please.

Dr. VERESHCHAGINA. This is an ultimate goal of both PDUFA and BsUFA programs, to make sure that the drug development process is efficient as possible and that FDA's review as expeditious as possible, and the system in place is predictable for sponsors and for patients because they can be sure that the process is moving in a timely manner, and they will have access to device and medications as soon as they can make that benefit-risk determination.

Mr. CURTIS. Thank you.

Mr. Gaugh?

Mr. GOUGH. Thank you for the question.

So as we talked earlier, Mr. Carter asked that question about getting generics to market, and of course, the innovator has to come to market first, and then we have to get through all the patents and the patent tickets to happen with those products.

Once that happens, we have now built into GDUFA III and specifically the product you are talking about would be in complex generics that would allow it to move through that process more quickly.

Mr. CURTIS. Thank you.

I mentioned this morning it is my hope we can put names and faces behind these people, and that might help us motivate to go quicker.

We had a biomedical innovation hearing in December in this very room right here, and I shared that ALS is a diagnosis that hits very close to me, as it did for many people in that room that day. I have lost too many good friends to this disease.

And so the times that we do not give patients enough flexibility to access and try therapies, despite urgency of a degenerative disease.

Dr. Ramachandran, you mentioned concerns over accelerated approval pathways. Let me just ask this. Keeping in mind that very personal nature of these diseases, if patients are made aware of the adverse risks, if they consent, if we acknowledge somewhat of a death sentence that they have been given, do you believe that they should be given the opportunity to access these treatments?

Dr. RAMACHANDRAN. Thank you, Congressman, for the question.

I definitely appreciate that viewpoint, having taken care of patients in which I am left kind of flustered in the exam room or in the hospital, not being sure what I can give them because there is really no option.

You know, to your point, you know, I understand that, you know, when patients are willing to accept the risk, there are pathways in which they can get access, and that is through an expanded access or through clinical trials.

And the reason why I think that pathway is important in order for them to get access is because we should be able to study whether or not the drug is actually working for them, whether it is, you know, clinically beneficial for them or they are actually feeling better.

And that way it can help inform a whole population of patients to see whether or not it would also be beneficial for them as well.

Mr. CURTIS. Thank you.

I do not deny the logic of what you are saying, but the sheer numbers of people who would like to try and do not have access

to what you have just described, I just want to leave a marker that is something that we ought to be thoughtful about.

I firmly believe in the importance of our ingenuity and innovation here in America, and we need to do all we can to foster it.

Ms. Reed and Dr. Esham, how can we clearly or more frequently engage with the agencies that show through interactive meetings or RDA pilots for rare disease help bring novel treatment to the market?

Ms. REED. So I think from a biosimilars perspective, we are working with the BsUFA III, but also have started working with the agency on a best practice for communications. So I think that is a great opportunity for industry.

But for members of the Congress, I, you know, encourage you to continue dialogues with the agency and follow up to say how is it going. Let's not wait every five years to find out how user fee programs are going. Let's ask—

I apologize because my time has expired and, Doctor, thank you for letting us pass on this. I am simply out of time.

And, Madam Chair, I yield my time.

Ms. ESHOO. OK. The gentleman yields back.

Boy, you sure made it under the wire.

[Laughter.]

Ms. ESHOO. Mr. Joyce, you are recognized for 5 minutes, and if we can do it in less time, it would be wonderful because we have votes on.

Mr. JOYCE. Thank you, Madam Chair.

And thank you to our distinguished panel for appearing here today.

This is an incredibly important issue, the safe, consistent, and prompt approval of pharmaceuticals, biologics, generics, biosimilars is critical to our health of our constituents.

I think I am going to go straight to the questions. What has been the general experience with the FDA's use of remote oversight tools?

Have these tools been effective? Do they facilitate adequate review and approval?

Mr. GAUGH, I will ask you to start.

Ms. REED. Yes, I will take that for biosimilars.

The FDA needs to improve its inspections of biosimilars. In my testimony I mentioned that biosimilar inspections are not a priority and not mission critical for the agency.

We have biosimilar applications and approvals that are delayed for over a year because of COVID. We need to see the agency prioritize biosimilars, use these remote tools, and use their staff that are on site in developing or different countries. They have people outside the U.S. that could help facilitate the use of the remote tools and the remote inspections. [Audio malfunction.]

Mr. JOYCE. In my whole State of Pennsylvania, I have heard from one company in particular, Nabriva Therapeutics, which has faced these delays, and they are seeking to bring to market in the United States a novel, first class therapeutic for the treatment of complicated urinary tract infections.

And unfortunately, due to these delays the drug is not approved in the United States.

Do you believe that there are steps that we can take to improve this process, especially taking into consideration what we have learned in COVID-19?

I will ask Dr. Esham.

Dr. ESHAM. OK. Happy to answer that question.

And I would say that, you know, we have long supported the increased use of expanded tools in the toolbox to meet the growing demands and complications of inspection activities.

The pandemic offered the opportunity of necessity to collect a lot of learning about how we could more effectively utilize more collaborations with foreign regulators, use of digital tools, and record of use, again, to mitigate against disruptions we were seeing during the pandemic.

I will note that it may be of interest in early 2021, BIO, PhRMA, AM, and PBOA met with the FDA to share its collective thinking about how we could utilize risk-based approaches for inspections and things, record requests.

And in the PDUFA agreement there are steps being taken, including the publication of guidance that we think will be very beneficial in advancing that thinking and expanding that toolbox.

Mr. JOYCE. And, Doctor Esham, in conclusion in the face of the time, that collaborative effort has to be so important. Americans expect the innovation that we look for to treat our patients.

I thank you, and I thank you, Madam Chair. I think we are going to all make it in time to vote.

Ms. ESHOO. And the gentleman yields back.

So that concludes our second panel. To each one of the witnesses, thank you. Thank you for your testimony. Thank you for the work that you have done, as it all related to the negotiations with the FDA to our purposes for us to move this legislation forward, and we will.

And we thank you, again, for your participation today.

So we have documents to submit for the record. So I request a unanimous consent to enter the documents into the record.

Mr. GUTHRIE. No objection.

Ms. ESHOO. No objections. That is wonderful.

Let's see. Without objection, so ordered.

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

Ms. ESHOO. And I should remind members if anyone is paying attention that they have ten business days to submit additional questions for the record to the witnesses.

Please respond promptly to any questions that you receive from members.

And at this time the subcommittee is adjourned.

[Whereupon, at 3:55 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

VIEWPOINT

Accelerated Approval Is Not Conditional Approval
Insights From International Expedited Approval Programs

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Accelerated approval was developed in the US in 1992 as an expedited regulatory approval pathway for drugs and biologics in response to the AIDS crisis. Since then, the US Food and Drug Administration (FDA) has granted the majority of accelerated approvals in oncology, leading to earlier availability of promising therapies for patients with cancer, a median of 3.4 years before completion of the confirmatory trials that would have been necessary for regular marketing approval.¹ Success of the US accelerated approval program has prompted other international regulatory health authorities (RHAs) to develop similar expedited approval programs (Table²). Although they share a goal of providing earlier access to potentially lifesaving therapies, critical differences exist, which we compare herein.

Accelerated Approval in the US

Accelerated approval was instituted in 1992 by regulation and was codified into law under the FDA Safety and Innovation Act in 2012.² This law allows for "approval of a product for a serious or life-threatening disease or condition ... [that] has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."³ Most accelerated approvals granted in oncology have relied on overall response rate as a primary endpoint.¹ However, overall response rate is not limited to accelerated approval and has been used to support regular approvals, particularly in rare disease settings, in those with long survivorship, and in cases where observed high response rates in initial trials would render subsequent randomized trials impractical owing to the loss of equipoise because of this prior efficacy data.

The FDA Safety and Innovation Act also specifies that accelerated approvals "may be subject to" the requirement "that the sponsor conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit."³ Several factors can affect the successful completion of these studies, including enrollment challenges and the rapidly evolving treatment landscape in oncology, which were addressed recently by an Oncologic Drugs Advisory Committee meeting in April 2021.⁴ Typically, if clinical benefit is verified by these postmarketing trials, then a regular approval is granted. However, if they are not conducted with due diligence or fail to verify clinical benefit, FDA may withdraw the accelerated approval indication, which can involve a lengthy process and include a public hearing if the applicant does not remove the indication voluntarily.³ This process has lasted up to 11 months (eg, first-line bevacizumab in com-

bination with paclitaxel for treatment of metastatic *ERBB2* [formerly HER2]-negative breast cancer). To date, 15 of 167 (8.9%) oncology indications granted accelerated approval have been withdrawn voluntarily (n = 14) or by FDA (n = 1).⁵

Promoting the timely completion of confirmatory trials can be a challenge after accelerated approval. In a recent analysis, the median time to verification of benefit was 3.4 years, whereas withdrawal took 8.8 years. Having an ongoing confirmatory trial at the time of accelerated approval was associated with a shorter median time to verification of benefit (3.1 vs 5.5 years).¹

International Expedited Approval Programs

Since development of the US accelerated approval program, expedited approval programs have been implemented by several international RHAs (Table). Most rely on endpoints that are likely to predict clinical benefit; however, conditional marketing authorization (CMA) in the European Union (EU) and UK relies on a benefit-risk assessment. This has led to relatively few approvals based on single-arm clinical trial data by the EU (52% for all indications).⁶ Another notable feature of programs in the EU, Switzerland, and UK is that only new molecular entities are considered for expedited approval. This contrasts with the US and others, which may also grant expedited approval for supplemental applications.

Additionally, unlike accelerated approval in the US, the expedited approvals granted by the EU, UK, Australia, and Switzerland are time limited and expire. In the EU and UK, CMA expires yearly and must be renewed with an application and interim report on outstanding obligations submitted at least 6 months before expiration.^{6,7} Evaluation of each renewal application includes the risk-benefit assessment as well as the time frame for completion of the specific obligations determined at the time of CMA. The mean time from granting CMA until conversion to a standard marketing authorization in the EU is 3.5 years.⁸ Similar to CMA, provisional approval in Australia expires after 2 years and may be extended for additional 2-year periods up to a maximum of 6 years. A fixed deadline may exclude trials with slow enrollment that require a long time to complete. In prior analyses of accelerated approvals and EU CMAs, the time from expedited approval to subsequent action was greater than 6 years in 21% and 27%, respectively.¹⁶ Temporary authorization in Switzerland also expires after 2 years and may be extended in exceptional cases. These programs in Australia and Switzerland were implemented recently (2018 and 2019, respectively), and data on time to verification are not yet available.

The expiry periods for conditional and provisional approval programs place the onus of timely completion of confirmatory trials and verification of benefit on the applicant in the EU, UK, Switzerland, and Australia. This contrasts with expedited programs elsewhere that place responsibility on

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Table. Comparison of International Expedited Approval Programs*

Regulatory health authority (country/union)	Expedited program (year initiated)	Eligible applications ^b	Postmarketing requirements	Approval expiration
US Food and Drug Administration (United States)	Accelerated approval (1992)	New molecular entities and supplements	Confirmatory trial that verifies the clinical benefit in the same or a related population	No
Health Canada (Canada)	Notice of Compliance with conditions (1998)	New molecular entities and supplements	Confirmatory trial(s) that verify the clinical benefit Annual progress reports of confirmatory trials and other ongoing trials Postmarketing surveillance	No (annual progress reports required until the conditions have been met or removed)
European Medicines Agency (European Union)	Conditional marketing authorization (2006)	New molecular entities	Complete specific obligations to confirm positive benefit-risk balance	Yes (valid for 1 y, must renew)
Pharmaceuticals and Medical Devices Agency (Japan)	Conditional approval (2017) ^c	New molecular entities and supplements	Confirmatory studies or other clinical data (including database-based studies) that reaffirm the clinical efficacy and safety in the target population	No
Therapeutic Goods Administration (Australia)	Provisional approval (2018)	New molecular entities and supplements	Continuation of trials Submission of confirmatory efficacy and safety data required for full registration within the provisional registration period	Yes (must be renewed every 2 y and completed in 6 y)
Swissmedic (Switzerland)	Temporary authorization (2019)	New molecular entities	Fulfillment of conditions determined at the time of approval	Yes (valid for 2 y, may be extended in exceptional cases)
Medicines and Healthcare Products Regulatory Agency (United Kingdom)	Conditional marketing authorization (2021)	New molecular entities	Complete specific obligations to confirm positive benefit-risk balance	Yes (valid for 1 y, must renew)

* Adapted from Friends of Cancer Research.²^b US Food and Drug Administration categories used for consistency.^c Regenerative medicine products (cell and gene therapy) are considered under the program Conditional, time-limited approval.

the RHA to initiate a resource-intensive withdrawal process. Overall, these time-limited approaches may limit public exposure to stale claims of effectiveness that cannot be expeditiously substantiated. Conversely, as reasonable trial completion times are often indication specific, flexibility may be necessary in implementing such postmarketing time limits.

Conclusions

The accelerated approval pathway in the US has allowed earlier access to lifesaving therapies for patients with cancer and has cre-

ated a model for other RHAs to develop similar expedited approval programs. More recently, the FDA Oncology Center of Excellence, through Project Orbis, has led efforts to coordinate regulatory processes between international RHAs to benefit patients with cancer worldwide.⁹ Future discussions of the accelerated approval program in the US can continue to build harmony between these agencies and strengthen this approval pathway by considering the differences between expedited programs, including recent innovations by international RHAs.

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REFERENCES

1. Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US Food and Drug Administration accelerated approval of malignant hematology and

oncology drugs and biologics: a review. *JAMA Oncol*. 2018;4(6):849-856. doi:10.1001/jamaoncol.2017.5618

2. Optimizing the use of accelerated approval. Friends of Cancer Research. 2020. Accessed December 13, 2021. https://friendsofcancerresearch.org/sites/default/files/2020-11/Optimizing_the_Use_of_Accelerated_Approval-2020.pdf

3. Food and Drug Administration Safety and Innovation Act, 21 USC §301 (2012). Accessed December 13, 2021. <https://www.govinfo.gov/content/pkg/PLAW-112publ44/pdf/PLAW-112publ44.pdf>

4. Beaver JA, Pazdur R. "Dangling" accelerated approvals in oncology. *N Engl J Med*. 2021;384(18):e68. doi:10.1056/NEJMp2104846

5. Withdrawn cancer accelerated approvals. US Food and Drug Administration. Updated December 3, 2021. Accessed December 15, 2021. <https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals>

6. Conditional marketing authorisation: report on ten years of experience at the European Medicines

Agency. European Medicines Agency. 2017. Accessed December 13, 2021. https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf

7. Provisional approval pathway: prescription medicines. Australian Government Department of Health, Therapeutic Goods Administration. March 20, 2018. Accessed December 13, 2021. <https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines>

8. Annual report 2020: the European Medicines Agency's contribution to science, medicines and health in 2020. European Medicines Agency. 2021. Accessed December 13, 2021. https://www.ema.europa.eu/en/documents/annual-report/2020-annual-report-european-medicines-agency_en.pdf

9. de Claro RA, Spillman D, Hotaki LT, et al. Project Orbis: global collaborative review program. *Clin Cancer Res*. 2020;26(24):6412-6416. doi:10.1158/1078-0432.CCR-20-3292

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Health Canada (Canada)	Notes of Compliance with Conditions (NCC) (1998)	New molecular entities and supplements	Confirmatory trials that verify safety and efficacy in the same or a related population	No (limited programs in which the conditions have been waived or shortened)
European Medicines Agency (European Union)	Conditional marketing authorization (2002)	New molecular entities	Postmarketing surveillance, confirmatory studies or other data demonstrating benefit-risk	Yes (not for 1 y, most for 2 y, may be renewed)
Pharmaceutical and Medical Devices Agency (Japan)	Conditional approval (2017)	New molecular entities and supplements	Confirmatory studies or other data demonstrating benefit-risk	No
Therapeutic Goods Administration (Australia)	Provisional approval (2018)	New molecular entities and supplements	Confirmatory studies or other data demonstrating benefit-risk	Yes (not for 2 y, may be renewed)
Swissmedic (Switzerland)	Priority authorization (2019)	New molecular entities	Confirmatory studies or other data demonstrating benefit-risk	Yes (not for 2 y, may be renewed)
Medicines and Healthcare Products Regulatory Agency (United Kingdom)	Conditional marketing authorization (2012)	New molecular entities	Confirmatory studies or other data demonstrating benefit-risk	Yes (not for 2 y, may be renewed)

Table Title:
Comparison of International Expedited Approval Programs^{a,b} Adapted from Friends of Cancer Research.
^b US Food and Drug Administration categories used for consistency
^c Regenerative medicine products (cell and gene therapy) are considered under the program Conditional, time-limited approval.

1/27/22, 4:12 PM

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Former FDA commissioner Scott Gottlieb (Photo by Mark Wilson/Getty Images)

January 27, 2022 01:39 PM EST

Updated 02:17 PM

Pharma

Scott Gottlieb criticizes CMS in feud over Aduhelm coverage, calls out their lack of expertise

Paul Schloesser
Associate Editor

Former FDA commissioner and [current Pfizer board member](#) Scott Gottlieb went on the offensive against CMS this morning — citing the agency’s “flawed decision making” and how the agency’s decision on Aduhelm is putting not just Alzheimer’s drug research in limbo but potentially setting a negative precedent for accelerated approvals.

Gottlieb, who was in charge of the federal agency from 2017-2019, talked with *BioCentury*’s Steve Usdin on how the precedent that CMS is setting could impact accelerated approvals outside of Alzheimer’s — and even further, blurring the lines of authority between the FDA and CMS.

RELATED: [UPDATED: CMS to restrict coverage of Biogen's controversial Alzheimer's drug to only clinical trials](#)

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RELATED: [Exclusive: Biogen president fears CMS will finalize restrictive coverage decision for Aduhelm, preps plans to flood NCD with comments](#)

Gottlieb, who spent some time in the early 2000s as a CMS senior advisor, said that the center's decision would create a lot of obstacles for patients.

The former FDA commissioner added:

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I think a lot of critics on the outside sort of applauded Medicare's muscular response in their coverage decision without really questioning the precedent that was getting set in the context of that decision. First of all, Medicare largely rejected the analysis of the FDA — didn't really condition its coverage decision on the FDA analysis — went out and sought a separate analysis from the NIH. They took the unprecedented position that because the drug was approved under accelerated approval, that it didn't necessarily prove an advantage and didn't necessarily need to be covered.

Gottlieb further drove the point on accelerated approvals, and that CMS' decision put pretty much the entire field of Alzheimer's drug research in limbo. He said that CMS is “now using the issue of whether or not a drug is approved under regular approval versus accelerated approval as a basis potentially going forward for denying coverage to drugs.”

And this led to Gottlieb's next point — since CMS pretty much said that the impact on cognition in the clinical trial isn't enough to merit approval, what impact would merit such approval? And since nobody knows where that line is, it leaves the entire field of Alzheimer's drug development in a state of limbo, in Gottlieb's view.

The comments from Gottlieb echo those released by Duke's Margolis Center for Health Policy, run by another former FDA commissioner Mark McClellan, from earlier this week on the draft NCD. The center asked CMS bluntly: “Can CMS clarify what evidence is needed for broader coverage of a particular mAb?”



Mark McClellan

Industry group PhRMA also argued the ethics of some receiving a placebo (and paying to receive a placebo) in the CMS-mandated trials, rather than an FDA-approved drug.

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“Nobody knows what the objective measure is that CMS is going to base its coverage decision around when it comes to improving cognition,” Gottlieb said. “Presumably because CMS doesn’t know they sort of denied this — said it wasn’t a robust enough effect on cognition, but didn’t say what they would judge to be a robust enough effect.”

Gottlieb continued in his critique of CMS’ decision, calling it “problematic to have a single agency inside Washington staffed by eight physicians who don’t have expertise in the areas that they’re adjudicating, making coverage decisions that are effectively binding across the entire market. Because every single private payer is going to ultimately peg its own decisions to the decision made by CMS.”

But many others have called the draft NCD a solid move by CMS, explaining that Biogen still hasn’t confirmed clinical benefit in a trial and therefore doesn’t merit widespread coverage yet.

Lon Schneider, who directs the University of Southern California’s State of California Alzheimer’s Disease Center, previously told Endpoints that the draft NCD was “a smackdown” as CMS “also told Lilly that FDA might give you AA [accelerated approval] or BTD [breakthrough designation] but we’ll wait to see positive trials results.”

The Aduhelm approval, which [originally failed](#) an 11-member adcomm back in 2020 before [being approved](#) last June, led to heated criticism that then led Medicare to decide to only limit reimbursement to patients in a clinical trial.

At the same time, Biogen is [attempting to coordinate](#) a backlash that would persuade Medicare to change course before it finalizes its coverage decision in April.

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FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics
February 3, 2022, 10:30 a.m.
United States House Committee on
Energy and Commerce
Randall L. Rutta
Chief Executive Officer

Chairwoman Eshoo, Ranking Member Guthrie, and Members of the Subcommittee on Health of the Committee on Energy and Commerce, on behalf of the National Health Council (NHC), I am writing to share our perspective on the reauthorization of user fee agreements (UFA) for fiscal years (FY) 2023-2027.

Background on the NHC

Created by and for patient organizations 100 years ago, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, sustainable health care. Made up of more than 140 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses representing biopharmaceutical, device, diagnostic, generic drug, and payer organizations.

We thank you for the opportunity to submit our recommendations ahead of the Congressional hearing and look forward to providing further support to continue innovating the regulatory framework on behalf of people with chronic conditions and disabilities across the United States (U.S.).

FY2023-2027 User Fee Reauthorizations

We are pleased to see Congress' efforts toward the reauthorization of the UFAs for FY2023-2027. We support the user fee goals outlined in the Food and Drug Administration's (FDA) Commitment Letters, which support timely reviews of products while ensuring a rigorous approach to determining safety and efficacy as well as demonstrate a focus on the patient perspective. As members of the Energy and Commerce Committee are aware, UFAs are an essential vehicle for ensuring FDA has needed capacity to review products and modernize the regulatory infrastructure, which is a critical mechanism for addressing many of the health care issues patients face today.

The importance of the user fee reauthorizations is particularly timely this upcoming cycle given the inequitable access to COVID-19 vaccines and treatments, weaknesses in the drug supply chain, and need for increased focus on comorbidities and minority populations in clinical trials. At the same time, health care stakeholders have seized opportunities for increasing the efficiency and transparency of the drug review process and modernizing clinical trial protocols, particularly through advanced technologies – processes that need to be firmly incorporated in the overall regulatory framework.



We hope that Congress will partner with the NHC to achieve our goals to further the science of patient engagement; elevate the voice of patients; and focus on more equitable research, development, and delivery of medical products. We are ready to provide any support necessary for the passage of the agreements. The NHC highlights some of the most important initiatives included in the FDA Commitment Letters for the next cycle:

Prescription Drug User Fee Act (PDUFA) VII¹

- **Patient Focused Drug Development (PFDD) Initiative:** Continued funding and development of the PFDD initiative will be key to ensure that the patient perspective is systematically incorporated in the drug development process. As such, we are pleased to see the inclusion of specific pathways for patient input and *urge Congress to ensure that this initiative remains a key focus of the next user fee cycle.*
- **Digital Health Technologies (DHTs):** Technology for data collection, storage, and transmission has advanced to harness a strong potential to provide a better picture of patient experience during a clinical trial with timelier and more direct information collection. If deployed appropriately, the technology can also benefit patients more directly by providing them with updates on the clinical trial process and transparency around the use of their data. Wearables and other remote monitoring devices can support drug developers and the FDA by reducing the significant burden of clinical trial participation, enhancing sponsors' ability to collect critical information from a broader, more diverse set of patients during clinical trials. While this area was a priority of the NHC before the COVID-19 pandemic, it has been even further elevated, as many sponsors had to modify their trial protocols to limit the frequency of trial site visits to protect participants from the virus, which potentially offers a treasure trove of lessons. The NHC applauds the FDA's commitment to developing a framework to evaluate the use of DHTs in clinical trials. *Specifically, we are pleased to see that FDA is committed to:*
 - Conducting demonstration projects, including engagement with stakeholders such as patients and patient organizations;
 - Convening a series of public meetings or workshops;
 - Establishing a cross-center committee with the role, among other priorities, of engaging stakeholders such as patient representatives; and
 - Creating a DHT framework document.
- **Advancing Real-World Evidence (RWE) Program:** Previous user fee programs have initiated the RWE Program, which has been instrumental in paving the way for incorporation of broader patient populations in the evaluation of drug products and has received particular attention in the development of COVID-19 vaccines and therapeutics. The PDUFA VII commitments are designed to further the science of RWE. The Program will provide drug developers and the FDA with flexibility for data collection methods that will go a far way to helping those suffering from chronic diseases gain access to critical medicines. RWE can also give us a more robust perspective on benefits of risks medical products on a broader population than limited clinical trial populations. *We strongly support development of the Advancing RWE Program, including FDA funding for new RWE pilots that will support the dissemination of lessons learned on the topic to patients and manufacturers.*
 - We further encourage Congress to consider enhancing the program by including provisions for researchers to engage patients, or leverage insights from patients, in the design, conduct, and translation of real-world

research such that patients' lived experiences are appropriately reflected in drug development.

Biosimilar User Fee Act (BsUFA) III and Generic Drug User Fee Amendments (GDUFA) III

While the BsUFA and GDUFA programs have not existed as long as PDUFA, they are equally critical in increasing affordable access to medicines for patients and have received similar attention as part of larger discussions around drug access in the U.S.

In particular, the availability of generic drugs has delivered tremendous savings to people with chronic conditions and disabilities, and to the health care system more broadly. With generic drugs comprising nine of 10 prescriptions filled in the U.S.², the GDUFA program requires significant resources and staff.

We encourage Congress to provide the FDA with the necessary funding and resources to be able to effectively manage the generic drug review process, enhance communication practices between the Agency and sponsors, and advance product-specific guidance, ultimately to increase timely generic availability.

Similarly, the BsUFA program is critical for providing clear and effective regulatory pathways to licensure of biosimilar and interchangeable biologics. These products, as with generics, provide cost-saving opportunities for patients and the U.S. health care system. The biosimilar industry, and its regulatory framework, is faced with unique development and manufacturing challenges compared to small-molecule drugs and generics. As a result, we would like to emphasize the importance for Congress to support initiatives outlined by the FDA focused on enhancing the biosimilar and interchangeable biological product development process and the use of advanced analytical and pharmacological assessments in application submissions.

Historical Importance of User Fee Agreements

The UFAs create a structure for the FDA, industry, and other health care stakeholders to ensure that patients have equitable access to life-saving medicines as rapidly and safely as possible, and that the patient voice is incorporated in the drug development and review process.

The UFAs were initially set up to facilitate access to medicines through a variety of mechanisms: they expedite FDA review of new medicines, devices, biosimilars, and generic drugs; increase resources for the Agency through sponsor and manufacturer fees; and create expectations on behalf of industry and the FDA for the drug development and review process. Past UFAs have been critical in modernizing our regulatory frameworks to focus on patients' needs through various programs and initiatives, such as:

- **PDUFA III** – Reauthorization initiated a “rolling review” pilot program for products addressing rare and life-threatening diseases (called the Orphan Drug Designation), which is an area that still needs significant attention as people continue to suffer without available treatments for rare diseases.
- **PDUFA V** – Under this reauthorization from 2012-2017, the FDA conducted 24 disease-specific Patient-Focused Drug Development (PFDD) meetings to obtain the patient perspective more systematically on specific diseases and their treatments.
 - The agreement also increased funding for the Rare Disease Program which, in later reauthorizations, was expanded by incorporating Program staff into each review division of the Agency.

- **PDUFA VI** – In the last PDUFA reauthorization, we saw the FDA build upon learnings from the PFDD meetings to produce guidance for industry and other stakeholders on collecting systematic patient experience data.
 - FDA also initiated its RWE Program by generating guidance on the use of real-world data (RWD) in the evaluation of safety and efficacy of products and regulatory decision-making.
 - FDA has also advanced guidance around the use of patient reported outcomes in regulatory submissions during this PDUFA period.

Conclusion

The NHC would like to thank the Subcommittee on Health and the entire Committee on Energy and Commerce for their work on the UFA reauthorizations that will help patients in the U.S. gain access to medicines in a timely and safe manner.

As we, hopefully soon, emerge from the COVID-19 pandemic, the agreements will be an imperative vehicle for modernizing our health care system and filling the gaps in care that still exist today. The NHC is ready to work with Congress in any capacity necessary on the issues pertaining to the user fee programs, as well as other topics affecting the health care industry. Thank you for the opportunity to provide the perspective of the NHC and, by extension, millions of people with chronic conditions and disabilities in the U.S.



Alzheimer's Association and Alzheimer's Impact Movement Statement for the Record

**United States House Committee on Energy and Commerce, Health Subcommittee
Hearing on "FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and
Biologics"**

February 3, 2022

The Alzheimer's Association and Alzheimer's Impact Movement (AIM) appreciate the opportunity to submit this statement for the record for the House Committee on Energy and Commerce, Health Subcommittee hearing on "FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics." The Association and AIM thank the Subcommittee for its continued leadership on issues important to the millions of people living with Alzheimer's and other dementia and their caregivers. As the Subcommittee works to reauthorize the user fee agreements, we particularly appreciate the focus on improving diversity in biomedical research. This statement highlights an important bipartisan bill within the Subcommittee's jurisdiction, the Equity in Neuroscience and Alzheimer's Clinical Trials (ENACT) Act (H.R. 3085/S. 1548), which would increase the diversity of Alzheimer's clinical trial participants to ensure all populations benefit from the latest scientific advances. This statement also highlights policies that would ensure timely access to safe and effective treatments.

The Alzheimer's Association is the world's leading voluntary health organization in Alzheimer's care, support, and research. It is the nonprofit with the highest impact in Alzheimer's research worldwide and is committed to accelerating research toward methods of treatment, prevention, and, ultimately, a cure. AIM is the advocacy affiliate of the Alzheimer's Association, working in strategic partnership to make Alzheimer's a national priority. Together, the Alzheimer's Association and AIM advocate for policies to fight Alzheimer's disease, including increased investment in research, improved care and support, and development of approaches to reduce the risk of developing dementia.

Alzheimer's Impact on American Families and the Economy

Alzheimer's is a progressive and fatal brain disorder that damages and eventually destroys brain cells, leading to a loss of memory, thinking, and other brain functions. There are no survivors.

Alzheimer's is emotionally, physically and financially draining for individuals and families. In addition, Alzheimer's is creating an enormous strain on the health care system, and federal and state budgets. The annual cost for caring for individuals living with Alzheimer's or other dementia will total \$355 billion including health care, long-term care, and hospice care in 2021. The U.S. taxpayer-funded federal health care programs Medicare and Medicaid are expected to cover \$239 billion, or 67 percent, of these costs this year. In addition, American families provide an estimated \$250 billion in unpaid care. While an estimated 6.2 million Americans age 65 and

older are currently living with Alzheimer's, nearly 13 million Americans will have Alzheimer's by 2050 and costs will exceed \$1.1 trillion (in 2021 dollars). Alzheimer's and other dementia threaten to bankrupt families, businesses, and our health care system.

Increasing Diversity in Alzheimer's Clinical Trials

A significant hurdle in developing therapeutics and care models for Alzheimer's disease that work for people of all ethnic and racial backgrounds is the recruitment and retention of traditionally underrepresented groups in clinical trials. Alzheimer's and other dementia disproportionately affect older Black and Hispanic Americans compared to older Whites. Black Americans are about twice as likely to develop Alzheimer's and Hispanic Americans are about one and a half times more likely to develop the disease. However, much of the Alzheimer's research to date has not included sufficient numbers of Blacks, Hispanics, Asian Americans/Pacific Islanders and Native Americans to be representative of the U.S. population. The underrepresentation of these populations not only hinders the ability of researchers to understand these health disparities, it also restricts their knowledge of how an approved therapy or diagnostic may affect the population most likely to need the treatment. There is therefore an urgent need for current and future research to include increased numbers of Blacks, Hispanics, Asian Americans/Pacific Islanders, and Native Americans in clinical trials to ensure everyone benefits from advances in Alzheimer's science.

According to the [*Alzheimer's Association 2021 Alzheimer's Disease Facts and Figures special report*](#), nearly two-thirds of Black Americans (62%) believe medical research is biased against people of color — a view shared by substantial numbers of Asian Americans (45%), Native Americans (40%), and Hispanic Americans (36%) as well. In fact, only half of Black Americans (53%) trust a future cure for Alzheimer's will be shared equally regardless of race, color or ethnicity. This underscores the need to build and restore trust in underrepresented communities. Strong community relationships can serve to address misconceptions and mistrust about research because the community has a sense of ownership in the research initiative.

The National Institute on Aging (NIA) has established a good foundation of centers across the country that offer local resources, support, and opportunities to participate in Alzheimer's and other dementia research. NIA currently funds over 30 Alzheimer's Disease Research Centers (ADRCs) at major medical institutions across the United States and four Exploratory ADRCs that are designed to expand and diversify research and education opportunities to new areas of the country, new populations, and new areas of science and approaches to research. There are also eight Alzheimer's disease-focused Resource Centers for Minority Aging Research (RCMARs) which focus on enhancing the diversity of the aging research workforce by mentoring promising scientists from underrepresented groups for sustained careers in aging research. These ADRCs and RCMARs are well-positioned to increase education and outreach activities to underrepresented populations within their communities.

The bipartisan **Equity in Neuroscience and Alzheimer's Clinical Trials (ENACT) Act (H.R. 3085/S. 1548)** would increase the participation of underrepresented populations in Alzheimer's

and other dementia clinical trials by expanding education and outreach to these populations, encouraging the diversity of clinical trial staff, and reducing participation burden, among other priorities.

Specifically, the ENACT Act would provide funding for NIA to expand the number of ADRCs in areas with higher concentrations of underrepresented populations, such as through entities like Historically Black Colleges and Universities (HBCUs), Hispanic-Serving Institutions, Tribal Colleges and Universities (TCUs), or centers of excellence for other underrepresented populations. The ENACT Act would provide funding for ADRCs and RCMARs to increase education and outreach to underrepresented communities and primary care physicians to let them know about current trial opportunities, the importance of participation, and the disparate impact of the disease on their populations. Importantly, ADRCs and RCMARs would use community-based engagement strategies in their outreach to underrepresented populations.

The ENACT Act would direct the NIA to enhance the diversity of principal investigators and study staff conducting Alzheimer's and other dementia clinical trials, so they are more representative of the populations they're trying to enroll. The bill directs the NIA to provide training to principal investigators from underrepresented populations on topics like clinical protocols and how to apply for grants, so they have the necessary expertise. NIA would also ensure senior researchers from underrepresented populations are included when making awards for leadership and excellence in Alzheimer's research.

The ENACT Act would reduce participation burden to make it easier for underrepresented populations to participate in Alzheimer's and other dementia clinical trials by providing incentives for locating Alzheimer's clinical trial sites in areas with high concentrations of underrepresented populations, as identified by data from the U.S. Census and Medicare claims data. The bill would direct NIA to ensure grantees use community-based engagement strategies in their outreach to underrepresented populations. The bill also encourages the use of remote health technology in communities, such as remote patient monitoring, to ease the burden of participation. Importantly, the bill would direct NIA to ensure grantees appropriately budget for outreach activities to underrepresented populations and include a description of outreach plans. NIA would also encourage grantees to engage with community-based organizations in efforts to increase clinical trial participation of underrepresented populations.

Finally, the ENACT Act would ensure inclusion and exclusion criteria are not unnecessarily restrictive so that older adults and individuals with a mild form of comorbid conditions are included, unless there is a strong clinical or scientific justification to exclude them. The bill also encourages the use of adaptive clinical trial design which could expand to include broader populations as the trial progresses through Phases I, II and III. This is important because Black and Hispanic Americans with Alzheimer's have higher rates of comorbid conditions, such as cardiovascular disease and diabetes, and these conditions should not unnecessarily disqualify these populations from participating in clinical trials. This is consistent with FDA's November 2020 guidance, ["Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry."](#)

We urge the Subcommittee to include this important bipartisan bill, which already has the support of many Subcommittee and Committee members, in a future legislative package and look forward to working with the Chair and Ranking Member as it moves through the legislative process. There is also growing support for the ENACT Act off the Hill: in addition to the Alzheimer's Association and AIM, groups that support this bipartisan bill include the AME International Health Commission, American Academy of Neurology, Black Nurses Rock, National Asian Pacific Center on Aging, National Caucus and Center on Black Aging, Inc., National Hispanic Council on Aging, National Hispanic Medical Association, National Indian Council on Aging, SAGE (Services & Advocacy for LGBT Elders), and UsAgainstAlzheimer's.

Accelerated Approval and Ensuring Timely Access to FDA-Approved Therapies

The accelerated approval pathway at the Food and Drug Administration (FDA) is critical to providing timely access to new, safe, and effective treatments to people living with serious and life-threatening diseases and conditions for which there are no meaningful alternatives. As Congress intended, this pathway allows for earlier access to drugs for these types of diseases while confirmatory evidence is being generated. As the Subcommittee works to reauthorize the user fee agreements, we ask that you consider a provision that would allow for the use of real-world evidence (RWE) to fulfill or support post-approval study requirements to confirm the predicted clinical benefit of a therapy approved through the accelerated approval pathway. In November 2021, the Alzheimer's Association, American College of Radiology, American Society of Neuroradiology, Department of Biostatistics at Brown University School of Public Health and other clinical research experts announced the formation of the [National Treatment and Diagnostic Alzheimer's Registry](#). This new national registry will be an FDA-approved-agent agnostic approach to gathering routine clinical practice data and outcomes from providers caring for patients diagnosed with Alzheimer's disease who are taking an FDA-approved disease-modifying treatment. Using data like this as RWE in post-approval study requirements could help facilitate the completion of more timely phase IV studies, and could yield greater insight to the therapy's impact on underrepresented populations and those with comorbid conditions - populations which may be harder to enroll in placebo-controlled trials.

Finally, we ask that you support improved and ongoing communication between the FDA and the Centers for Medicare & Medicaid Services (CMS) with regard to breakthrough therapies, fast track products, and those eligible for accelerated approval.

Conclusion

The Alzheimer's Association and AIM appreciate the steadfast support of the Subcommittee and its continued commitment to advancing legislation important to the millions of families affected by Alzheimer's and other dementia. We look forward to working with the Subcommittee on the FDA user fee reauthorizations and urge you to advance the bipartisan ENACT Act (H.R. 3085/S. 1548) to increase the diversity of Alzheimer's clinical trial participants and ensure future approved therapies and diagnostics are safe and effective for the populations most likely to need the treatment.



Statement for the Record
American College of Physicians
Hearing before the House Energy and Commerce Subcommittee on Health
“FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics”
February 3, 2022

The American College of Physicians (ACP) is pleased to submit this statement and appreciates that Chairman Pallone and Chairwoman Eshoo are holding this hearing to examine legislation reauthorizing user fee agreements, which allow for the timely review and approval of medications by the U.S. Food and Drug Administration (FDA). These agreements are set to expire this year and they are vital to ensuring the safety and efficacy of medications in this country. We hope that this important hearing will lead to broader bipartisan discussions to increase access to necessary and often life-saving prescription drugs and treatments for patients at an affordable cost. We are pleased to offer our perspective on underlying policies applicable to the three legislative proposals under consideration today, as they pertain to brand name prescription drugs, generic drugs, and biosimilar drugs.

The American College of Physicians is the largest medical specialty organization and the second-largest physician membership society in the United States. ACP members include 161,000 internal medicine physicians (internists), related subspecialists, and medical students. Internal medicine physicians are specialists who apply scientific knowledge and clinical expertise to the diagnosis, treatment, and compassionate care of adults across the spectrum from health to complex illness. Internal medicine specialists treat many of the patients at greatest risk from COVID-19, including the elderly and patients with pre-existing conditions like diabetes, heart disease and asthma.

ENSURING SAFE AND EFFECTIVE MEDICATIONS

Prescription drug development is a complex process that includes the discovery and development of new drug compounds, research, testing, review, approval, and post marketing surveillance. According to the Biotechnology Innovation Organization, the United States produces more new drugs (57 percent) than the United Kingdom, Japan, Germany, and France combined (28 percent), as noted in ACP’s 2020 [position paper](#) entitled, *Policy Recommendations to Promote Prescription Drug Competition*.

The FDA follows a very rigorous [process](#) to ensure that all medications are safe and effective for consumers, and this includes an accelerated approval process to bring innovative drugs and devices to market faster through [user fee](#) agreements with manufacturers. User fees are paid by biopharmaceutical and medical device companies to facilitate the agency’s regulation and

review of prescription drugs, generic drugs, and medical devices. User fees have grown to provide the FDA with nearly half of its [\\$6 billion budget](#). Without these resources, the FDA would be forced to significantly curtail the number of prescription drugs and other medical products it reviews each year.

Americans look to the FDA as the gold standard for getting life-sustaining and life-saving medications to consumers in a safe, effective, and timely way. This has never been more evident than during the global fight against the coronavirus and the development of vaccines and treatments to combat it. ACP believes it is vital to improve the FDA's ability to approve and monitor prescription drugs through increased funding and support efforts to regulate drugs manufactured outside the U.S. through both appropriations and user fees. ACP opposes any efforts to weaken FDA authority to demand rigorous evaluations of drugs and medical devices for both safety and effectiveness based on sound scientific and medical evidence and opposes legislative attempts to curtail FDA authority to establish and maintain standards of safety and effectiveness for approval of drugs and medical devices. We must realign incentives that reward true innovation, prevent manufacturers from exploiting loopholes, and address business practices that lead to increased costs to the health care system. This will increase the availability of lower-cost drugs in the marketplace, lower out-of-pocket costs for patients, and help drive down the price of prescription drugs.

Prescription Drug User Fee Amendments of 2022 (PDUFA)

PDUFA was created by Congress in 1992 and authorized the FDA to collect fees from companies that produce certain human drug and biological products. Since the passage of PDUFA, user fees have played an important role in expediting the drug approval process. On August 16, 2021, the FDA announced the [Prescription Drug User Fee Rates](#) for Fiscal Year 2022 in the Federal Register. These fees apply to the period from October 1, 2021, through September 30, 2022. The PDUFA of 2022 would reauthorize user fees for prescription drugs for an additional five years.

- **Transparency:** ACP urges the subcommittee to consider including in PDUFA Title IV of the *Elijah E. Cummings Lower Drug Costs Now Act* (H.R. 3). This title establishes mandatory reporting requirements applicable to manufacturers if they increase the price of a prescription drug by 10 percent or more over a 12-month period, or by 25 percent or more over a 36-month period, or if the estimated price of a qualifying drug for an applicable year per course of treatment is at least \$26,000. ACP policy supports transparency in the pricing, cost, and comparative value of all pharmaceutical products. Pharmaceutical companies should disclose actual material and production costs to regulators, research and development costs contributing to a drug's pricing, including those drugs which were previously licensed by another company. Rigorous price transparency standards should be instituted for drugs developed from taxpayer-funded basic research.

- **Advertising:** ACP urges the subcommittee to consider including in PDUFA the *End Taxpayer Subsidies for Drug Ads Act* (S. 141). This legislation would prohibit a tax deduction for expenses for direct-to-consumer advertising of prescription drugs, thus eliminating the deduction that pharmaceutical companies use to pay for drug advertising. ACP believes that direct-to-consumer advertising of prescription drugs is an inappropriate practice that undermines the patient-physician relationship and often leaves patients confused and misinformed about medications. The FDA should play a stronger role in ensuring that complete, valid, and clear information is provided to the public and in making determinations about whether the commercial information in a DTC ad actually will educate and enhance the health of the public. Furthermore, Congress should give the FDA the authority to issue regulations that require review and approval of the content of any DTC advertisement prior to it being released to the public.

Generic Drug User Fee Amendments of 2022 (GDUFA)

GDUFA was created by Congress in 2012 to ensure patients have access to safe, high-quality, and affordable [generic drugs](#). GDUFA enables the FDA to assess industry user fees to bring greater predictability and timeliness to the review of generic drug applications. On July 28, 2021, the FDA announced the [Generic Drug User Fee Rates for Fiscal Year 2022](#) in the Federal Register. These fees apply to the period from October 1, 2021, through September 30, 2022. The GDUFA of 2022 would reauthorize user fees for generic drugs for an additional five years.

ACP urges the subcommittee to consider including in GDUFA the *Protecting Consumer Access to Generic Drugs Act of 2021* (H.R. 153). This legislation would prohibit brand name drug manufacturers from compensating generic drug manufacturers to delay the entry of a generic drug into the market (pay-for-delay) and would prohibit biological product manufacturers from compensating biosimilar and interchangeable product manufacturers to delay entry of biosimilar and interchangeable products. ACP policy supports robust oversight and enforcement of restrictions on product-hopping, evergreening, and pay-for-delay practices as a way to increase marketability and availability of competitor products. ACP believes applicable federal agencies should be empowered through guidance, congressional action, or additional resource support to address anticompetitive behaviors and gaming.

Biosimilar User Fee Amendments of 2022 (BsUFA)

BsUFA was created by Congress in 2012 and authorized the FDA to assess and collect fees from drug companies that submit marketing applications for certain [biosimilar biological products](#). On July 28, 2021, the FDA announced the [Biosimilar Drug User Fee Rates for Fiscal Year 2022](#) in the Federal Register. These fees apply to the period from October 1, 2021, through September 30, 2022. The BsUFA would reauthorize user fees for biosimilars for an additional five years.

Biosimilar drugs are products that have only minor variations in clinically inactive components versus biologic (reference) products and have no clinically meaningful differences in safety,

purity, or potency compared with a reference product. In a sense, they offer the same benefits of generic drugs. However, because they are developed from a biological source rather than a chemical entity, are not approved under an abbreviated new drug application (ANDA) and are not considered interchangeable unless they meet the additional criteria for interchangeability from the FDA, biosimilars are not considered “generics” of biologic reference products. The Affordable Care Act included provisions to encourage market competition for biosimilar drugs. As part of the ACA, biologic drugs are awarded 12 years of combined data and marketing exclusivity during which no biosimilar can enter the market.

ACP urges the subcommittee to consider including in BsUFA a provision to reduce the period of data and market exclusivity for biologic drugs from 12 years to seven years. ACP also supports removing additional barriers to biosimilar market entry, such as modifications to the current patent system that would reduce excessive patenting on brand-name and biologic drugs.

STRENGTHENING THE SUPPLY CHAIN OF VITAL MEDICATIONS

ACP also urges the subcommittee to consider additional measures germane to this hearing to help the federal government respond to future pandemics, including facilitating the procurement and availability of pandemic-related vaccines and other antiviral medications in the Strategic National Stockpile. The FDA has always played a central role in the federal response to public health emergencies.

ACP supports the national procurement of vaccines in an amount sufficient to protect the entire U.S. population and national procurement of antiviral medications to cover 25 percent of the U.S. population. ACP believes that additional courses of antiviral medications should be safeguarded in the Strategic National Stockpile for all public safety officers and health care workers with direct patient contact in amounts sufficient to provide prophylaxis. In the event of a pandemic, stockpiled vaccines and antivirals should be distributed equitably to all states’ public health authorities based on the numbers of people in high-risk and high-priority groups.

ACP is encouraged by draft legislation currently under consideration in the Senate Health, Education, Labor & Pensions Committee entitled the PREVENT Pandemic Act that addresses the need for this improved readiness. Specifically, ACP supports the following provisions as outlined in that draft legislation:

- Title I would establish a 12-member “National Task Force on the Response of the United States to the COVID–19 Pandemic” that would review the United States’ response to the COVID-19 pandemic. ACP believes it is essential that the commission include physicians with expertise in pandemic preparedness and response, including primary care physicians who have been on the frontlines of treating patients with COVID-19.
- Title IV would improve coordination and communication among private sector entities and the FDA to ensure that medical countermeasures can be rapidly manufactured when needed to respond to public health emergencies.

- Title V would clarify FDA’s authority to consult with third parties to evaluate and make recommendations with respect to the validity, accuracy, and reliability of in vitro diagnostic tests for use during a public health emergency, which will enable the FDA to prioritize its response efforts where needed during future emergencies.
- Title V provides the FDA with authority to share more safety and effectiveness information with the public about products authorized for emergency use.

CONCLUSION

We appreciate this opportunity to offer our input on legislative proposals before this subcommittee to reauthorize user fee programs within the FDA. As lawmakers deliberate on these important policies, we urge you to keep in mind what is in the best interests of patients and their ability to access high quality, affordable medications. Should you have any additional questions, please contact Jonni McCrann at jmccrann@acponline.org.

Attachment—Additional Questions for the Record

**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "**
February 3, 2022

Patrizia Cavazzoni, M.D.,
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

The Honorable G.K. Butterfield (D-NC)

1. Newborn screening is vital for disrupting the diagnostic odyssey for children with rare, genetic disorders by diagnosing them at birth. The Health Resources and Services Administration's ("HRSA") Advisory Committee on Heritable Diseases in Newborns and Children ("ACHDNC") is tasked with updating the Recommended Uniform Screening Panel ("RUSP") to help guide states in operating their newborn screening programs. Alarming, following the Pompe disease addition to the RUSP in 2013, the ACHDNC has *only* added three conditions the RUSP – mucopolysaccharidosis ("MPS") type 1, spinal muscular atrophy, and X-linked adrenoleukodystrophy. Moreover, several similarly rapidly progressing rare disorders with FDA-approved therapies, including cerebrotendinous xanthomatosis, CLN2, Fabry disease, MPS II, MPS IVA, and MPS VI, are *still* not on the RUSP. Such delays are a direct result of the ACHDNC Evidence-Based Review Group only considering disorders for addition to the RUSP if there is data from newborn screening pilot studies involving population-based screening of identifiable newborns with the proposed condition and availability of an effective treatment. It is my understanding that the pilot study requirement is particularly onerous and expensive. The bureaucracy that has slowed the RUSP clearly needs an overhaul in order to keep pace with drugs and biologicals currently in development that would be the first ever FDA-approved therapy for rapidly progressive and fatal disorders caused by an inherited or de novo genomic alteration or abnormality, such as Canavan disease, CLN1, CLN3, CLN5, CLN7, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease, metachromatic leukodystrophy, MPS IIIA, IIIB, and IIC, Niemann-Pick type C, Sandhoff disease, and Tay-Sachs disease.

- a. From your perspective, how has the lack of newborn screening affected clinical trial enrollment for these investigational therapies?

Diagnostics that are approved, cleared, or authorized by FDA and that can safely and effectively screen newborns can help health care professionals identify and discuss potential treatment options with parents and caregivers before symptoms or effects on a baby's health may be noticeable.

Diagnostics can also help to identify potential patients to be considered for clinical trial enrollment. However, clinical trial enrollment criteria generally include a specific diagnosis and other criteria, such as signs and symptoms of disease. Given that clinical trials generally have various enrollment criteria,¹ it is challenging to directly comment on the impact of newborn screening on clinical trial enrollment.

- b. What role should FDA play to ensure the tremendous work being done by its review divisions in approving therapies that are satisfying unmet need for rare pediatric diseases can benefit these children? For example, would you recommend coordination between FDA and HRSA to ensure the ACHDNC is aware of investigational breakthrough therapies that are in clinical development for non-RUSP conditions for which screening presents a high likelihood of significant public health benefit and value through the reduction of time to diagnosis?**

We welcome dialogue with HRSA and appreciate the question about sharing information with HRSA's Advisory Committee. Consistent with applicable law, including federal statutes and FDA's regulations, and to protect the integrity of the review process, FDA generally cannot publicly disclose information about an unapproved application, including the existence of specific unapproved applications for investigational new drug or biologic products. There are limited exceptions to these restrictions on FDA's ability to discuss pending applications; and the availability for disclosure of information would be made in the context of a particular unapproved application, taking into account all relevant facts and applicable laws.

- c. Do you think the underpinnings of the FDA's accelerated approval pathway for drug review could be applied to the RUSP process by allowing for "preliminary inclusion" on the RUSP upon the submission of an NDA or BLA for breakthrough therapy designated drugs or biologics seeking approval for a rare pediatric disease not currently on the RUSP, but for which a validated assay exists, until further evidence, including real world evidence, is generated to support full RUSP inclusion?**

Generally speaking, FDA is not in a position to make recommendations regarding the Recommended Uniform Screening Panel process.

¹ For example, requiring certain signs or symptoms upon which the investigational therapy may claim to have an effect.

The Honorable Lisa Blunt Rochester (D-DE)

- 1. The coronavirus outbreak exposed our fragile medical supply chains. Pandemic-related drug shortages challenged our country's ability to ensure that patients had reliable access to essential generic medications. What role will supply chain security play in the future of medical product approvals?**

Pandemic-related supply issues have included increased demand which led to shortages for certain medications needed for hospitalized patients, as well as shortages due to competition for limited manufacturing capacity at facilities making both vaccines and other COVID-related products on lines that also make other drugs. Another example of a recent pandemic-related shortage is the IV Contrast agent shortage caused by the shutdowns in China.

FDA is taking a number of actions to help improve the reliability of the supply chain and limit shortages. The Coronavirus Aid, Relief, and Economic Security (CARES) Act amended the Federal Food, Drug, and Cosmetic (FD&C) Act to require that manufacturers of certain prescription drugs or active pharmaceutical ingredients (API) or associated medical devices used for preparation or administration included in the drug shall develop, maintain and implement, as appropriate, a redundancy risk management plan that identifies and evaluates risks to the supply of the drug. The CARES Act also amended the FD&C Act to require FDA to prioritize and expedite, as appropriate, the review of certain applications that could help mitigate or prevent a shortage of certain critical drugs, including generic drugs. For instance, in calendar year 2021, to help increase patient access to critically needed medications in shortage or to prevent potential shortages, FDA expedited reviews for close to 100 original abbreviated new drug applications (ANDAs) and over 100 ANDA supplements. Moreover, for pandemic-related shortages, reviews of applications for additional manufacturers of these critical drugs are expedited as are reviews of applications for any changes manufacturers need to make to increase production (e.g., new facilities, manufacturing lines and suppliers).

In addition, FDA is gaining greater insight into the supply chain through implementation of the requirement added by the CARES Act that manufacturers submit annual reports to FDA regarding amounts of drug manufactured for commercial distribution. FDA has issued draft guidance and developed a portal to facilitate submission of that data. These data will be integrated with other internal data to provide insights into supply chain and risks.

FDA will continue to take all available steps working with manufacturers to minimize the risk of shortages and supply chain disruptions.

- 2. As noted in your testimony, in March 2020, the U.S. Food and Drug Administration (FDA) announced the creation of the Coronavirus Treatment Acceleration Program (CTAP), an emergency review and development program for COVID-19 treatments. The Agency supported the program by reassigning staff and working continuously to review requests from companies and researchers working to develop therapies. What additional authorities, regulatory flexibilities or resources would**

enable the FDA to quickly respond to future emergency situations, while meeting key PDUFA commitments and preventing staff burn out?

FDA's existing authorities are sufficiently flexible and adequate to enable a robust response to a public health emergency while meeting key PDUFA commitments. Critical to our success during the COVID-19 pandemic was additional funding provided by Congress to secure the resources necessary for our pandemic response. For FDA to remain nimble in the face of future public health emergencies, adequate funding and resources will be critical.

- 3. Alzheimer's and other dementia disproportionately affect older Black and Hispanic Americans compared to older White Americans. However, much of the Alzheimer's research to date has not included sufficient numbers of Black, Hispanic, Asian Americans/Pacific Islanders and Native Americans to be representative of the United States population. FDA has issued guidance on how to enhance the diversity of clinical trials, like ensuring clinical trial eligibility criteria are not unnecessarily restrictive and encouraging the use of adaptive clinical trial design. I've introduced a bipartisan bill with Representatives Herrera Beutler, Curtis, Smith, and Waters, the ENACT Act, to increase the participation of underrepresented populations in Alzheimer's and other dementia clinical trials, which includes these FDA recommendations. The bill would also expand education and outreach to these populations, encourage the diversity of clinical trial staff, and reduce trial participation burden, among other priorities. How important is it to ensure the population enrolled in Alzheimer's trials reflects the population most likely to need access to future treatments?**

FDA has a long-standing commitment to promoting diversity and inclusion of underrepresented populations in clinical trials. Inclusion of diverse populations likely to reflect the patient populations that will use the drug if approved can help increase our understanding of the benefit-risk profile of investigational drugs. A more diverse clinical trial population can make labeling of therapeutic products more informative for healthcare providers and patients and enhances patient safety. Enrollment of diverse populations in clinical trials may also potentially minimize the need for postmarketing studies. We note that Alzheimer's disease is most prevalent in older adult populations and that populations generally become more heterogeneous with advancing age. Therefore, enrolling diverse populations in Alzheimer's trials is important for ensuring that future treatments are safe and effective for patients affected by this disease.

As noted in your question, in November 2020, FDA published the final guidance [Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial-designs)², which discusses broadening eligibility criteria and avoiding unnecessary exclusions for clinical trials, when medically appropriate and scientifically sound. This guidance is one among several guidance documents addressing diversity in clinical trials.

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial-designs>

Although progress has been made to increase the enrollment of diverse populations, there is still room for improvement. One strategy that has not been scaled up in a sustainable way is engaging community clinicians and investigators in research. There is considerable evidence that clinician recommendations play an important role in helping patients consider participating in clinical investigations.³ In addition to clinicians' recommendations playing an important role, removing barriers to participation, such as bringing trials closer to where participants live, work, worship, and typically receive their healthcare, may also help achieve more diversity in both the workforce administering the trials and the participants undergoing investigative treatment. Decentralizing clinical trials, such as by providing access to them outside of academic research settings, could be an effective mechanism to improve diverse representation by bringing trials into communities.⁴

The Honorable Brett Guthrie (R-KY)

- 1. One of the commitments outlined in the PDUFA agreement is to further improve how real-world data is collected and used. The data used in such studies, however, is not always generated by individual drug sponsors. Given that real-world data is often generated by other organizations who specialize in this work, do you agree that they should be included in the proposed pilot program to improve the quality and acceptability of RWE?**

- a. How else does FDA intend to engage with leading organizations that develop real-world data outside of the context of a specific drug development program?**

The focus of the Advancing RWE Program is on identifying approaches for generating real-world evidence that can meet regulatory requirements in support of claims or to support or satisfy post-approval study requirements, which are completed by sponsors. Therefore, the Advancing RWE Program is designed for sponsors. However, FDA has several other pathways to engage with real-world data providers and has done so successfully. These pathways included direct meetings with the Center for Drug Evaluation and Research's (CDER's) RWE Subcommittee and funding of demonstration projects.

- 2. Knowledge management and information sharing is extremely important across FDA Centers. What types of knowledge management activities have CDER and CBER established?**

Enabling comprehensive knowledge management to capture, retrieve and utilize institutional knowledge is of paramount importance to FDA. CDER and the Center for Biologics Evaluation and Research (CBER) have a number of established capabilities and in-progress initiatives supporting their knowledge management needs. CDER's informatics strategy connects a modernized workflow management capability, master data management, and a broad analytics platform to support a connected flow of information through data receipt,

³ <https://www.nejm.org/doi/full/10.1056/NEJMp2107331>

⁴ See, for example, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6072894/>

regulatory review, and analytics activities. CDER One, leveraged by both CDER and CBER, is a cloud-based enterprise data lake and analytical platform to provide a robust environment to underpin some of its knowledge management activities. CDER One brings data together from internal and external sources to support analytics needs across all review areas. The expanding CDER Nexus modernized workflow management capability provides a robust, process-focused workflow environment to support consistency of business processes and bringing together stronger collaborative authoring processes. As part of its ongoing modernization efforts, CDER's Office of New Drugs (OND) and CBER have established governance and processes to continually monitor and refine their strategy and program data domains and to assure integration with broader CDER and CBER knowledge management. These efforts focus on greater consistency of data capture and integration of knowledge across disciplines and the review programs through data governance, standardized and structured review templates and workflow enabled processes.

CBER and CDER are actively engaged and collaborating in FDA's implementation of an overarching Data and Technology strategy that includes new and expanding initiatives to support effective knowledge and information sharing across FDA. This work will connect with and augment program-focused capabilities. Several efforts include:

- FDA's Intelligent Data Lifecycle Ecosystem (FiDLE) – FiDLE is FDA's enterprise-wide ecosystem, designed to meet cross-center data management, advanced data science and analytics platform needs.
 - Enterprise data catalog – An initiative across Centers to establish an organized inventory of data assets within FDA to help organizations and data professionals manage, collect, organize, access, and enrich their data to support discovery and governance.
 - Global Substance Registration System – a database of highly curated substances within regulated products. This system currently interfaces with several FDA pre- and post-market systems to enable association of substances to products, applications, clinical trials, and adverse events for biologics, drugs and cosmetics.
3. **In the last quarter of 2020, FDA issued a series of four RWE draft guidances, providing recommendations on assessing electronic health records, claims data, and registries for regulatory use. The guidances reflect the Agency's incremental approach to RWE, focusing on using RWE to support new indications of previously approved drugs. Recently, CDER announced plans for additional guidances in their 2022 guidance agenda on use of RWE to support drug development and regulatory decision making. However, use of RWE to support regulatory approvals for unapproved drugs has been limited. How can the use of RWE advance to the point of supporting new regulatory approvals for unapproved drugs?**

FDA defines real-world data (RWD) as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources", and real-world evidence (RWE) as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD". Because data from routine clinical practice would not typically be available for unapproved drugs, we would not expect RWE to be available to

support new approval of investigational drugs. However, RWD is still useful for purposes such as providing insights into the natural history of a disease or informing efficient trial design. These approaches may be especially important in the rare disease area where the study populations are small and available therapies are lacking, making it difficult to conduct traditional randomized trials. In these contexts, RWD on patients with the disease can potentially be used as a control arm for a single arm trial to inform FDA's assessment of the effectiveness of the intervention. Indeed, one of our guidance documents ([*Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry*](#)⁵) is particularly relevant to that use.

The Honorable Michael C. Burgess, M.D. (R-TX)

1. **One of the commitments outlined in the PDUFA agreement is to further improve how real-world data is collected and used. The data used in such studies, however, is not always generated by individual drug sponsors. Given that real-world data is often generated by other organizations who specialize in this work, do you agree that they should be included in the proposed pilot program?**
 - a. **How does the FDA plan to engage with leading organizations that develop real-world data outside of the context of a specific drug development program?**

The advancing RWE pilot program included in the PDUFA VII commitment letter (pending enactment of the reauthorization legislation) is designed for enhancing interaction with the Agency for specific development programs. However, organizations that may be contributing their data to the specific development program under consideration can be included in relevant meetings with FDA at the sponsor's discretion. Beyond the PDUFA program, FDA's RWE Subcommittee meets with non-sponsor organizations to provide insight into characteristics of RWD that are important in establishing data quality. Many of the related concepts are captured in our guidance on [*Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products*](#).⁶ Organizations can contact the Agency with questions regarding this draft document or the Real World Evidence Program by emailing CDERMEDICALPOLICY-RealWorldEvidence@fda.hhs.gov.

The Honorable H. Morgan Griffith (R-VA)

1. **What is the process FDA uses to solicit stakeholder input prior to the rollout of REMS programs?**

⁵ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products>

⁶ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory>

FDA is limited in the extent to which it can solicit stakeholder input prior to approval or implementation of a risk evaluation and mitigation strategy (REMS), because the Agency cannot publicly disclose information about applications that are under review. In some cases, FDA may receive stakeholder input when an application is brought before an Advisory Committee.

Due to the limitations on the Agency's ability to directly solicit stakeholder input, FDA strongly encourages the drug applicant(s) to seek input from stakeholders prior to submitting a REMS proposal and throughout the development and review process. The Agency urges applicants to consider how the proposed REMS will fit into the workflow of the health care providers that are impacted by the REMS and what actions can be taken to minimize burden to stakeholders.

2. Are there statutory changes FDA needs to ensure that REMS programs do not adversely impact patient access, incur unintended risks to patients, and increase burdens on healthcare providers and systems?

When REMS are not implemented effectively and efficiently, patient access to these products can be impacted.

Section 505-1 of the FD&C Act authorizes FDA to require a REMS for prescription drug products if necessary to ensure that the benefits outweigh the risks. While FDA can require manufacturers to implement certain activities under a REMS that support the safe use of the drug, such as periodic lab tests, certification of prescribers and pharmacies, or administration of the drug in a health care setting, the statute does not address specific methods for implementing or operationalizing these requirements.

Because the manufacturers are responsible for developing and implementing REMS and because the risks that are the subject of a REMS vary, standardization across different REMS has been limited and, in general, REMS are not well-integrated into existing healthcare delivery system workflows or health information technology (HIT) systems. This lack of integration and REMS data sharing across the healthcare delivery system creates burdens for providers and barriers to patient access and efficient communication about the risks of the drug and the REMS requirements. Legislative changes could help to clarify FDA's authority to require specific methods of implementation that better integrate REMS requirements into healthcare system workflows and HIT systems.

The Honorable Gus Bilirakis (R-FL)

- 1. Dr. Cavazzoni, the FDA's testimony mentions the most recent GDUFA legislation required Priority Review to become available for applications for generic drugs with limited competition, as well as for generic drugs in shortage. These provisions were a direct result of legislation I co-led with Representative Schrader, the Lowering Drug Costs through Competition Act. This bill also created the Competitive Generic Therapy (CGT) program, and I was pleased to see in the fall that FDA has approved over 100 generic drug applications with CGT designation.**

This means we are starting to see more competition in the marketplace, which will help alleviate prices. Can you explain how this next GDUFA proposal will build upon the successes of these programs for generics with little to no competition in the market? Can you explain why marketing exclusivity for CGT-designation has provided additional incentives for companies to establish generics with little or no competition in the market?

Under the anticipated reauthorization of Generic Drug User Fee Agreement (GDUFA), we will continue to prioritize certain applications for generic drugs with limited competition, consistent with criteria under section 505(j)(11) of the FD&C Act (as added by the FDA Reauthorization Act of 2017), and with CDER's Manual of Policies and Procedures (MAPP) 5240.3, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, available at <https://www.fda.gov/media/89061/download>.

The GDUFA III commitments also include several enhancements that are aimed at increasing generic competition by reducing the number of assessment cycles for ANDAs and facilitating timely access to generic medicines. For example, the enhancements include more opportunities for applicants to engage in meetings with FDA to help facilitate their development of generic drugs and FDA's review of their ANDAs and enhancements to our regulatory science program to help support development of more complex products. The commitments also contain enhancements that would help speed the resolution of quality manufacturing issues for generic drugs, including to facilitate resolution of inspectional issues, new goals for re-inspections, and additional opportunities for meetings between FDA and applicants.

You also asked about competitive generic therapies (CGTs) and the incentive provided by the potential for CGT-exclusivity for companies to market generics with little to no competition. From what FDA has observed, generic companies are actively participating in the program and seeking CGT designations, presumably because of the potential to receive exclusivity. In addition, the structure of this exclusivity – which only blocks the approval of other applications once the product with exclusivity is marketed and which is forfeited if the applicant eligible for exclusivity does not begin marketing in a timely manner post-approval – has been very successful at encouraging applicants to make their CGTs available to consumers quickly post-approval.

The Honorable Larry Bucshon, M.D. (R-IN)

- 1. Aside from the “Four Part Harmony” approach to CMC communication and the CMC Readiness Pilot outlined in the PDUFA VII goals letter, are there other strategies that the CDER and CBER intend to employ to improve communication on CMC issues?**

The PDUFA VII goals letter includes a robust set of activities to improve FDA and industry communication on chemistry, manufacturing and control (CMC) issues. This includes the items noted in your question, along with staff training on CMC assessment processes associated with mid-cycle and late-cycle review meetings with the goal of ensuring that mid-

cycle and late-cycle meeting expectations are met, including communicating the status of the NDA and BLA CMC assessment and any identified issues that would preclude approval.

In addition, CBER and CDER periodically examine communication approaches internally and formally (e.g., as part of communications assessment in previous PDUFA commitments). We update internal Manual of Policies and Procedures (MAPPs), Statements of Organization Practices and Procedures (SOPPS), Q&As, and guidance on communication to reflect more efficient and effective processes and practices, share best practices and train staff on communication practices. Furthermore, information requests to applications, including those for CMC issues undergo review at various levels for content and clarity. Increases in staffing, and retention of existing staff can also facilitate communication by having trained and experienced subject matter experts to discuss technical topics.

The Honorable Richard Hudson (R-NC)

- 1. Given the FDA’s Center for Drug Evaluation and Research (CDER) modernization efforts and the reorganization of the New Drug Regulatory Program, which includes a restructuring of the Office of New Drugs, please explain your vision for the new Division of Rare Diseases and Medical Genetics (DRDMG), particularly any new review processes CDER is considering and how CDER is working towards increased consistency in the application of current regulatory approaches to support rare disease drug development.**

Providing consistency in the application of regulatory approaches to expedite rare disease drug development was a founding principle for the new Division of Rare Diseases and Medical Genetics (DRDMG). Over the past two years, several new initiatives have been launched to further this goal:

- The rare disease consultation service was reconfigured to ensure that review staff from DRDMG with direct responsibility for rare genetic disease drug development are available to advise other review divisions as needed regarding novel trial designs for small sample sizes and best practices for considerations related to regulatory flexibility in rare disease drug development.
- The Rare Disease Drug Development Council was established. This council convenes multidisciplinary rare disease experts from across CDER, including from the Office of New Drugs (such as, DRDMG) and the Office of Translational Science, to discuss cross-cutting challenges in rare-disease drug development. The council has provided a platform for consensus building on these issues across CDER.
- DRDMG initiated the Zebragram, which is an internal newsletter that highlights practical examples from review divisions across CDER, Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) for advancing rare disease drug, device, and biological product development. The Zebragram has featured information regarding the use of novel trial designs, endpoints, and statistical approaches, and regulatory flexibility. This

type of tool helps to support rare disease product development through enhanced collaboration and communication.

- This spring, CDER launched the Accelerating Rare Disease Cures (ARC) Program, which will drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

As we work to promote rare disease considerations across CDER, one of the early lessons learned from these efforts is that collaboration and knowledge sharing are important as is a recognition of the unique scientific considerations within a specific disease area. For example, the kinds of strategies that work best to advance drug development for rare, rapidly progressing diseases with objective endpoints, like some cancers, blood disorders, or infections, might be different from the kinds of strategies that work best for rare, slowly progressive diseases with patient reported outcome endpoints, like many neurodegenerative or rare metabolic diseases. Our efforts support knowledge sharing and recognition of the scientific and regulatory considerations relevant to specific disease areas, which is facilitating rare disease product development.

- 2. FDA issued the Framework for FDA’s Real-World Evidence (RWE) Program in 2018. In the last quarter of 2020, FDA issued a series of four RWE draft guidance’s, providing recommendations on assessing electronic health records, claims data, and registries for regulatory use. The guidance’s reflect FDA’s incremental approach to RWE, focusing on using RWE to support new indications of previously approved drugs. In CDER’s Guidance Agenda for 2022, CDER announced plans for additional guidance’s on the use of RWE to support drug development and regulatory decision making. This is welcome news as the current use of RWE to support regulatory approvals appears extremely limited. It is my understanding that, to date, the July 2021 approval of a new indication for Prograf is the only approval based solely on RWE. Please explain CDER’s vision and plans to transition and better utilize RWE to move towards the overarching goal of supporting increased regulatory approvals.**

We are increasingly seeing sponsors submit RWD as an external control arm for a single-arm trial or to supplement their clinical trial data, and RWE has served as confirmatory evidence for applications seeking to establish substantial evidence of effectiveness through one adequate and well-controlled clinical investigation plus confirmatory evidence when appropriate. Prograf (tacrolimus) was notable in that the primary evidence for effectiveness came from RWE, but FDA’s confidence was bolstered by the results of randomized controlled trials in other solid organ transplant settings and by the natural history of a transplant (e.g., 100 percent mortality) in the absence of immunosuppressive therapy, such as Prograf, and other factors. Accordingly, we see RWE as potentially providing important evidence depending on the population and disease of interest, the research question(s), and the relevance and reliability of the data sources. We also see opportunities to generate RWE through randomized clinical trials that are more integrated into clinical practice, representing a model that was leveraged during the pandemic (e.g., in the RECOVERY trial). Such a model may also have the added benefit of being more inclusive of diverse study populations.

- 3. Throughout the COVID-19 pandemic, FDA has understandably been delayed in inspecting pharmaceutical manufacturing facilities for safety reasons. However, we are now more than two years into the pandemic and FDA’s latest report, An Update to the Resiliency Roadmap for FDA Inspectional Oversight – November 2021, indicates only 37 foreign inspections for human drugs were completed between April and September 2021. Please provide insight as to FDA’s plans to overcome the growing backlog and ensure inspections remain timely.**

As you have noted, in March 2020, at the beginning of the COVID-19 pandemic, FDA paused most foreign and domestic surveillance inspections in compliance with Federal guidelines to reduce the spread of the COVID-19 virus. Nevertheless, the Agency continued mission-critical inspectional work. In addition, FDA utilized several alternative oversight approaches to help ensure the availability of safe medicines. In July 2020, after developing a COVID-19 Advisory Rating system (COVID-19 Advisory Level), FDA resumed and prioritized certain domestic inspections across all commodities.

Since October 1, 2021, FDA has been conducting domestic inspections at pre-COVID-19 operational levels. This includes addressing surveillance inspections that were postponed during COVID-19. In February 2022, FDA resumed foreign surveillance inspections and pre-approval and pre-license inspections that were not initially identified as mission critical or otherwise prioritized during the COVID-19 pandemic.

FDA is committed to continue its return to a consistent state of operations as expeditiously as possible. As always, FDA will first focus on the most critical public health work and prioritize other responsibilities, including product-specific pre-approval and pre-license inspections, based on risk. FDA is developing and implementing strategies to address the postponed surveillance inspections. These strategies include reprioritizing drug inspections based on our review of records and information that firms provided under section 704(a)(4) of the FD&C Act, and refining the way the risk-based Site Selection Model is applied to prioritize sites for surveillance inspection. In addition, to maximize the use of our inspectional resources, FDA has begun to add surveillance inspection coverage to pre-approval, pre-license, and post-approval inspections, where appropriate. The Agency seeks to optimize the use of its existing inspectional authorities and use other oversight tools to maximize the public health impact of its resources.

In the same report, FDA cites the use of “new oversight approaches” and “expanded use of a variety of surveillance tools” as reasons that FDA was able to exceed its Base-Case Scenario projections for domestic surveillance oversight activities for FY 2021. Please provide specific insight and details as to how FDA is currently utilizing these and additional alternative tools to ensure patient access to medicines is not further delayed.

The Agency expanded its use of Remote Regulatory Assessments (RRAs), which include voluntary remote interactive evaluations (such as remote livestreaming video of operations, teleconferences and screen sharing) and requests to review records and other information

under statutory authority. In addition, FDA has relied upon reviewing trusted foreign regulator inspection records under existing Mutual Recognition Agreements (MRAs).

These alternative tools have enabled the Agency to better meet its oversight responsibilities when traveling and in-person contact were restricted. Throughout the pandemic, FDA has used these tools, domestically and abroad, to help the Agency conduct oversight, mitigate risk, and meet critical public health needs.

Specifically, RRAs have helped FDA to verify that firms have taken promised corrective actions in response to findings from previous inspections and in gaining compliance insight when it was not practicable to inspect. RRAs have provided information about deficient practices, which led FDA to take regulatory actions and conduct inspections, and have informed future inspection planning. RRAs have also been used to help support, and reduce delays of, approval or authorization of marketing submissions for FDA-regulated products during the COVID-19 pandemic. Since the start of the pandemic, FDA has initiated over 1,000 RRAs to assess establishments engaged in manufacturing operations for human drugs. These assessments have enabled FDA to assess compliance with Current Good Manufacturing Practice (CGMP), and supported assessments and approval decisions for drug applications.

While these activities are not inspections under Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act, they can be used in combination with other oversight approaches to provide FDA investigators and supporting subject matter experts with a means to assess compliance with CGMP regulations, and the degree of process and product control at a site where product related operations are taking place or have taken place.

FDA will continue to use these alternative tools in appropriate circumstances beyond the pandemic to help ensure patient access to medicines and ensure the safety and integrity of the supply chain.

According to same report, there was also an increase in the number of drug applications that were delayed solely because of an overdue inspection – specifically, the number increased from 48 to 52 between May and September 2021. Please explain how FDA is prioritizing the resumption of foreign inspections and the growing backlog of affected applications, including any specific criterion applied. In addition, please provide FDA’s expected timeline to fully resume foreign inspections.

Since October 1, 2021, FDA has been performing domestic inspections as per normal operations and in February 2022 resumed foreign surveillance inspections and pre-approval and pre-license inspections that were not initially identified as mission critical or otherwise prioritized during the COVID-19 pandemic. The specific criteria applied for determining the prioritization of inspections are outlined in Table 6 of the May 2021 Resiliency Roadmap for FDA Inspectional Oversight. This document states that mission critical inspections are to be performed first, which includes application approval inspections for high priority products, followed by for-cause application approval inspections (non-mission critical) and compounding inspections, and then routine surveillance and post approval inspections. As

FDA works through the inventory of postponed surveillance inspections, the Agency is prioritizing higher-risk establishments. For example, a sterile manufacturing site that has not been previously inspected and is making therapeutic index drugs would likely be deemed a higher risk than a site that had a well-known inspectional and compliance history that is making solid oral dosage form drugs. This means that postponed inspections will be prioritized based on risk and conducted on a schedule that allows FDA to strategically focus on products that present the greatest risk to public health.

FDA continues to make progress to facilitate and conduct inspections delayed or postponed due to the COVID-19 pandemic and strategies have been established to ensure that postponed facility inspections are risk assessed for prioritization.

The Agency continues to proceed with previously planned foreign surveillance inspections that have received country clearance and are within the CDC's Level 1 or Level 2 COVID-19 travel recommendation and has resumed surveillance inspections and pre-approval inspections that were not initially identified as mission critical.

The Honorable Earl L. “Buddy” Carter (R-GA)

- 1. Dr. Cavazzoni, the biggest challenge faced by sponsors at FDA with respect to rare disease therapies are the lack of expertise on review teams with respect to the rare disease under review and the lack of knowledge and experience with rare diseases generally among different review divisions, which can lead to inconsistencies in sponsor experience and prolong the review process to the detriment of the patient. It is well-established that rare disease therapy sponsor experience is inconsistent across review divisions at CDER. From your perspective, what can be done at CDER to ensure each review division is well informed about each rare disease or condition under review, including phenotypes, rate of progression, and current standard of care? Do you believe it is feasible to conduct comprehensive training for all FDA product review staff on rare disease drug development?**

The Rare Diseases Team in CDER, Office of New Drugs (OND) coordinates with CBER, CDRH, and the Office of Orphan Product Development in the Office of the Commissioner to collaborate on annual staff training to share learnings and promote rare disease education regarding policy and review across the Agency. In addition, the Rare Diseases Team hosts quarterly seminars presented by internal and external experts to train and inform staff on timely and important aspects of rare disease drug development relevant to their work on rare disease applications. Trainings encompass both broad topics important across rare diseases (e.g. complex innovative design use in rare diseases) and innovative topics or policies (e.g. new scientific innovation in gene editing or new FDA guidance on the use of real world data/evidence). Trainings include illustrative case studies, and are recorded and made available to FDA staff after the events to ensure access and availability.

OND has also established a new Rare Disease Drug Development Council comprised of leaders from across CDER's OND and from CDER's Office of Translational Sciences with expertise and experience in rare disease drug development to promote organizational

cohesion across rare disease issues and drug development programs. CBER and other Centers also participate in this new council. These types of approaches will further enhance collaboration, consistency, and knowledge sharing between OND divisions and across CDER and FDA, while ensuring that each rare disease drug development program is evaluated by staff that have the disease-specific expertise needed to appropriately design and evaluate these programs.

The Honorable John Joyce, M.D. (R-PA)

1. Will the FDA and IPMG commit to seeking stakeholder input prior proposing any substantial changes to the Clozapine and iPLEDGE REMS programs going forward?

While FDA can require manufacturers to implement elements under a REMS that are necessary for the safe use of the drug, such as periodic lab tests, certification of prescribers and pharmacies, or administration in a health care setting, the manufacturer determines the specific methods for implementing or operationalizing them. However, FDA encourages manufacturers responsible for implementing a REMS to seek stakeholder input from patient organizations and key professional organizations on the potential impact of REMS modifications to change third-party vendors engaged by sponsors to aid in implementation of the strategies. We will continue to recommend sponsors take public input into account to achieve continuity and minimize disruption when undertaking changes that could impact REMS management.

2. Who will be responsible for the rollout of program adjustments in the future? And how will the FDA hold them accountable?

Manufacturers are responsible for implementing the REMS for products that are subject to REMS requirements and the rollout of any program adjustments (i.e., modifications) approved by FDA. For new products approved with a REMS, the REMS must be operational for the drug to be introduced into interstate commerce.

Based on recent experience with the unsatisfactory implementation of modifications to the Clozapine and iPLEDGE REMS, we have asked other manufacturers that are currently proposing REMS modifications that involve changes in third-party vendors engaged by manufacturers to aid in implementation and management of the strategy, to perform a Failure Mode and Effect Analysis (FMEA) before implementation. The FMEA would identify potential failures and a proposed contingency plan to address such circumstances. Our primary objectives are to support a smooth transition and to prevent interruptions in treatment for patients.

The Agency believes it is important to hold manufacturers accountable for the efficient and smooth implementation of a REMS and any subsequent modifications.

3. Will there be test runs for future program changes before rolling them out to the general public for physicians, pharmacists, and patients?

FDA does and will continue to recommend that, prior to informing the public of a new or modified REMS program, manufacturers seek stakeholder input and test any platforms that will be used.

4. Will stakeholders (professional organizations representing physicians and pharmacists) be provided a direct point of contact to work with and respond to questions and concerns in a timely manner?

Stakeholders with questions may contact the applicable product center (CBER, CDER, etc.) for that particular REMS.

Although FDA does not administer the product-specific REMS programs, FDA's Division of Drug Information (DDI) is a resource that is available for stakeholders and professional organizations if they have questions, concerns, or want to report an issue about a particular REMS program. This resource was a particularly helpful mechanism for FDA to hear about stakeholder concerns related to the implementation of modifications to third-party vendors in the Clozapine and iPLEDGE REMS.

5. How can we ensure physicians, pharmacists and patients across the country have full proper access to the Clozapine and the iPLEDGE program?

FDA strives to ensure stakeholders have access to all REMS programs without undue burden, including the Clozapine and iPLEDGE REMS. The goal is to maintain patient access while still preserving safe use of a drug.

Due to implementation issues, stakeholder access was impacted by the modifications to the iPLEDGE and Clozapine REMS. The modifications to these programs were necessary due to a change in the REMS vendor for both programs. The Clozapine REMS modification required stakeholders to recertify, and the iPLEDGE REMS required previous certified and enrolled stakeholders to update their log-in accounts. For both programs there were significant challenges with implementing these modifications. As the implementation of the changes to these REMS have begun to stabilize, stakeholders have been more successful in accessing the REMS programs, but the issues have not been entirely eliminated.

6. How can we ensure that the FDA and REMS do not reinstitute provisions of the REMS that risk interrupted treatment and result in harm to patients?

Since December 2021, FDA has been temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for

patients taking clozapine.⁷ The Agency is analyzing metrics about the implementation of the Clozapine REMS and considering whether implementation issues affecting patient access to the medication have been addressed. Despite allowing additional time for stakeholders to enroll and certify, we have heard that some stakeholders will not certify in the REMS until it is absolutely necessary (e.g., once the enforcement discretion ends). Our highest priorities are continuity of care, patient access, and patient safety.

7. How can we ensure that the FDA does not reinstitute provisions of the REMS such as retroactive reporting of data that are not clinically useful?

The Clozapine REMS requires enrollment of all patients into a patient registry. The data collected through the registry, including repeated absolute neutrophil count (ANC), time to onset of neutropenia (if applicable), patient demographics, and patient health outcomes, can be used to evaluate the impact and frequency of the ANC monitoring. This information can be used to determine if changes are needed for labeling or the REMS to improve safety or reduce burden. While we believe this information will be very helpful, FDA does not intend to require retroactive reporting of ANC values and other information in the patient registry that was not collected during the period of enforcement discretion.

⁷ FDA is temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine, available at <https://www.fda.gov/drugs/drug-safety-and-availability/fda-temporarily-exercising-enforcement-discretion-respect-certain-clozapine-rems-program>.

Attachment—Additional Questions for the Record

**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "**
February 3, 2022

Peter Marks, M.D., Ph.D.,
Director, Center for Biologics Evaluation and Research,
U.S. Food and Drug Administration

The Honorable G.K. Butterfield (D-NC)

1. Newborn screening is vital for disrupting the diagnostic odyssey for children with rare, genetic disorders by diagnosing them at birth. The Health Resources and Services Administration's ("HRSA") Advisory Committee on Heritable Diseases in Newborns and Children ("ACHDNC") is tasked with updating the Recommended Uniform Screening Panel ("RUSP") to help guide states in operating their newborn screening programs. Alarming, following the Pompe disease addition to the RUSP in 2013, the ACHDNC has *only* added three conditions the RUSP – mucopolysaccharidosis ("MPS") type 1, spinal muscular atrophy, and X-linked adrenoleukodystrophy. Moreover, several similarly rapidly progressing rare disorders with FDA-approved therapies, including cerebrotendinous xanthomatosis, CLN2, Fabry disease, MPS II, MPS IVA, and MPS VI, are *still* not on the RUSP. Such delays are a direct result of the ACHDNC Evidence-Based Review Group only considering disorders for addition to the RUSP if there is data from newborn screening pilot studies involving population-based screening of identifiable newborns with the proposed condition and availability of an effective treatment. It is my understanding that the pilot study requirement is particularly onerous and expensive. The bureaucracy that has slowed the RUSP clearly needs an overhaul in order to keep pace with drugs and biologicals currently in development that would be the first ever FDA-approved therapy for rapidly progressive and fatal disorders caused by an inherited or de novo genomic alteration or abnormality, such as Canavan disease, CLN1, CLN3, CLN5, CLN7, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease, metachromatic leukodystrophy, MPS IIIA, IIIB, and IIC, Niemann-Pick type C, Sandhoff disease, and Tay-Sachs disease.

- a. From your perspective, how has the lack of newborn screening affected clinical trial enrollment for these investigational therapies?

Diagnostics that are approved, cleared, or authorized by FDA and that can safely and effectively screen newborns can help health care professionals identify and discuss potential treatment options with parents and caregivers before symptoms or effects on a baby's health may be noticeable.

Diagnostics can also help to identify potential patients to be considered for clinical trial enrollment. However, clinical trial enrollment criteria generally include a specific diagnosis and other criteria, such as signs and symptoms of disease. Given that clinical trials generally have various enrollment criteria,¹ it is challenging to directly comment on the impact of newborn screening on clinical trial enrollment.

- b. What role should FDA play to ensure the tremendous work being done by its review divisions in approving therapies that are satisfying unmet need for rare pediatric diseases can benefit these children? For example, would you recommend coordination between FDA and HRSA to ensure the ACHDNC is aware of investigational breakthrough therapies that are in clinical development for non-RUSP conditions for which screening presents a high likelihood of significant public health benefit and value through the reduction of time to diagnosis?**

We welcome dialogue with HRSA and appreciate the question about sharing information with HRSA's Advisory Committee. Consistent with applicable law, including federal statutes and FDA's regulations, and to protect the integrity of the review process, FDA generally cannot publicly disclose information about an unapproved application, including the existence of specific unapproved applications for investigational new drug or biologic products. There are limited exceptions to these restrictions on FDA's ability to discuss pending applications; and the availability for disclosure of information would be made in the context of a particular unapproved application, taking into account all relevant facts and applicable laws.

- c. Do you think the underpinnings of the FDA's accelerated approval pathway for drug review could be applied to the RUSP process by allowing for "preliminary inclusion" on the RUSP upon the submission of an NDA or BLA for breakthrough therapy designated drugs or biologics seeking approval for a rare pediatric disease not currently on the RUSP, but for which a validated assay exists, until further evidence, including real world evidence, is generated to support full RUSP inclusion?**

Generally speaking, FDA is not in a position to make recommendations regarding the Recommended Uniform Screening Panel process.

The Honorable Brett Guthrie (R-KY)

- 1. One of the commitments outlined in the PDUFA agreement is to further improve how real-world data is collected and used. The data used in such studies, however, is not always generated by individual drug sponsors. Given that real-world data is**

¹ For example, requiring certain signs or symptoms upon which the investigational therapy may claim to have an effect.

often generated by other organizations who specialize in this work, do you agree that they should be included in the proposed pilot program to improve the quality and acceptability of RWE?

a. How else does FDA intend to engage with leading organizations that develop real-world data outside of the context of a specific drug development program?

The focus of the Advancing RWE Program is on identifying approaches for generating real-world evidence that can meet regulatory requirements in support of claims or to support or satisfy post-approval study requirements, which are completed by sponsors. Therefore, the Advancing RWE Program is designed for sponsors. However, FDA has several other pathways to engage with real-world data providers and has done so successfully. These pathways included direct meetings with the Center for Drug Evaluation and Research's (CDER's) RWE Subcommittee and funding of demonstration projects.

2. Knowledge management and information sharing is extremely important across FDA Centers. What types of knowledge management activities have CDER and CBER established?

Enabling comprehensive knowledge management to capture, retrieve and utilize institutional knowledge is of paramount importance to FDA. CDER and the Center for Biologics Evaluation and Review (CBER) have a number of established capabilities and in-progress initiatives supporting their knowledge management needs. CDER's informatics strategy connects a modernized workflow management capability, master data management, and a broad analytics platform to support a connected flow of information through data receipt, regulatory review, and analytics activities. CDER One, leveraged by both CDER and CBER, is a cloud-based enterprise data lake and analytical platform to provide a robust environment to underpin some of its knowledge management activities. CDER One brings data together from internal and external sources to support analytics needs across all review areas. The expanding CDER Nexus modernized workflow management capability provides a robust, process-focused workflow environment to support consistency of business processes and bringing together stronger collaborative authoring processes. As part of its ongoing modernization efforts, CDER's Office of New Drugs (OND) and CBER have established governance and processes to continually monitor and refine their strategy and program data domains and to assure integration with broader CDER and CBER knowledge management. These efforts focus on greater consistency of data capture and integration of knowledge across disciplines and the review programs through data governance, standardized and structured review templates and workflow enabled processes.

CBER and CDER are actively engaged and collaborating in FDA's implementation of an overarching Data and Technology strategy that includes new and expanding initiatives to support effective knowledge and information sharing across FDA. This work will connect with and augment program-focused capabilities. Several efforts include:

- FDA’s Intelligent Data Lifecycle Ecosystem (FiDLE) – FiDLE is FDA’s enterprise-wide ecosystem, designed to meet cross-center data management, advanced data science and analytics platform needs.
 - Enterprise data catalog – An initiative across Centers to establish an organized inventory of data assets within FDA to help organizations and data professionals manage, collect, organize, access, and enrich their data to support discovery and governance.
 - Global Substance Registration System – a database of highly curated substances within regulated products. This system currently interfaces with several FDA pre- and post-market systems to enable association of substances to products, applications, clinical trials, and adverse events for biologics, drugs and cosmetics.
3. **Dr. Marks, in 2019, you and then Commissioner Gottlieb stated FDA’s intent to maximize the use of expedited programs and that, for gene therapy products, accelerated approval, in particular, represents an opportunity to meet this significant unmet need.**
- a. **Three years later, as gene therapies have advanced (despite the ongoing pandemic), how do you plan to realize these opportunities for use of accelerated approval?**

FDA is committed to facilitating the development of gene therapy products to address the unmet needs of people with serious and life-threatening diseases. In 2019, FDA released guidance around expedited programs for regenerative medicine therapies for serious conditions.² This guidance describes the expedited programs available to sponsors of regenerative medicine therapies for serious conditions, including those products designated as Regenerative Medicine Advanced Therapies (RMATs). To that end, the guidance provides information about the provisions in the 21st Century Cures Act (“Cures”) regarding the use of the accelerated approval pathway for regenerative medicine therapies that have been granted designation as an RMAT. Finally, the guidance describes considerations in the clinical development of regenerative medicine therapies and opportunities for sponsors of such products to interact with CBER review staff.

Since 2019, CBER has approved six CAR-T gene therapies for treatment of hematological malignancies, a directly administered gene therapy for spinal muscular atrophy, a fatal pediatric disease, and three tissue engineered products, one for the repair of single or multiple symptomatic full-thickness cartilage defects of the knee, one for the treatment of adults with thermal burns, and one for immune reconstitution in pediatric patients with congenital athymia. CBER is committed to using its full

² *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry*. 84 FR 4825 (February 19, 2019), available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions>.

breadth of programs, including RMAT and accelerated approval, for eligible products. To this end, CBER has licensed three products with RMAT designation.³

FDA, the National Institutes of Health (NIH), 10 pharmaceutical companies and five non-profit organizations have partnered to accelerate development of gene therapies for the 30 million Americans who suffer from a rare disease. While there are approximately 7,000 rare diseases, only two gene therapy products have been approved by FDA to treat rare diseases caused by specific gene mutations. The Bespoke Gene Therapy Consortium (BGTC), part of the NIH Accelerating Medicines Partnership (AMP) program and project-managed by the Foundation for the National Institutes of Health (FNIH), aims to optimize and streamline the gene therapy development process to help fill the unmet medical needs of people with rare diseases.

b. How are you striking the right balance between pre- and post-approval data generation?

To determine the appropriate balance of pre-approval data and post-approval data for each specific drug or biologic, FDA carefully reviews the safety and efficacy results gathered during drug development. The appropriate balance may depend on those results, the specific clinical indication, and the unmet medical need. FDA utilizes our expedited programs to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of serious or life-threatening conditions. One example of FDA's use of post-approval data are accelerated approvals, which are based on a determination that the product has an "effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit."⁴ Post-marketing confirmatory trials have then been required to verify and describe the predicted effect on the clinical benefit.

Additionally, when approving a drug or biologic product, FDA can impose a post-marketing requirement (PMR), which are studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use. PMRs can be required to assess a known serious risk or signals of a serious risk related to the use of the drug or biologic, or identify an unexpected serious risk when available data indicate the potential for a serious risk.⁵ Also, sponsors may agree to conduct studies and clinical trials after approval as a postmarketing commitment (PMC).

³ CBER Regenerative Medicine Advanced Therapy (RMAT) Approvals, available at <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cber-regenerative-medicine-advanced-therapy-rmat-approvals>.

⁴ Section 506 of the FD&C Act.

⁵ Section 505(o)(3)(B) of the FD&C Act; see also *Postmarketing Requirements and Commitments*, available at: <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments>.

FDA follows the science and makes these decisions, sometimes after seeking input from an Advisory Committee, on a case-by-case basis, to ensure that we fulfill our mission to both protect patient safety and bring new, innovative therapies to market.

c. How will you ensure that any changes aimed at improving the clarity and rigor of the accelerated approval process will not upset this delicate balance and still benefit patients today?

The accelerated approval pathway has been in existence for thirty years and has worked well to ensure the safety and efficacy of products approved by FDA. Changes to this pathway that would lower the evidentiary standard would decrease protections for patient health and likely compromise public trust in therapies granted accelerated approval. However, FDA believes there are changes that could be made to the accelerated approval pathway that could help advance the timely completion of post-approval studies required for the accelerated approval of drugs and biological products and clarify the process for any subsequent withdrawal of such approval. Enhancing the timeliness and quality of confirmatory studies would help support FDA's regulatory decision-making for drugs approved through the accelerated approval pathway and minimize the time that a product is marketed based on accelerated approval before its clinical benefit can be confirmed. These types of changes would improve the clarity and rigor of the accelerated approval pathway and would not upset the balance that protects patients today.

The Honorable Michael C. Burgess, M.D. (R-TX)

- 1. In its commitment letter, FDA retained language from prior letters stating that the Agency's major dispute resolution goals apply to "procedural or scientific matters." However, in 2017, FDA issued a separate [guidance document](#) on Formal Dispute Resolution that allows formal disputes only for "scientific and/or medical significance," thus excluding some procedural matters. Procedural matters are important, as you know, and ultimately, patients lose out if innovators cannot resolve issues with FDA in a timely manner.**

a. In light of FDA's PDUFA VII language on dispute resolution, will the Agency commit to revising its 2017 guidance to align to the PDUFA VII commitments you are making now, in particular to ensure procedural matters?

We appreciate your question about the Formal Dispute Resolution Program and agree that procedural matters are important and that innovators should have a path available to resolve procedural disputes, should they arise. CDER and CBER have current mechanisms in place to provide innovators a pathway for open and prompt discussion and resolution of procedural disputes. As outlined in the 2017 guidance document for the Formal Dispute Resolution Program, "...if a sponsor challenges specific

administrative and/or procedural decisions that arise during the course of an FDR, CDER and CBER intend to review these interim decisions as part of the review of the pending substantive scientific and/or medical dispute, and not as a separate review.” Procedural matters may also be raised with the appropriate Center ombudsmen. The CDER and CBER ombudsmen informally investigate and facilitate resolution of such issues.

2. Can we count on increased engagement from senior leaders at FDA in more routine meetings with sponsors to generate a more constructive and efficient dialogue?

a. Are there plans to better facilitate engagement and communication?

FDA recognizes the value of direct engagement between its senior leadership and sponsors. We do assure that appropriate senior staff are present at meetings. However, given the volume of meetings (e.g., 4,558 in fiscal year 2021), there are inherent limitations regarding scheduling and availability for both sponsors and FDA senior staff. There are opportunities for senior leadership input into drug development programs and engagement with sponsors outside of meetings, such as public workshops and advisory committees.

Sponsors will have access to additional engagement and communication with FDA’s expert scientific staff via some of the proposed PDUFA VII enhancements. Examples include the new Type D meeting, INTERACT meeting, and the follow-up opportunity following sponsor meetings that confirms understanding of the communications that took place. Similar changes are also proposed with respect to biosimilar and interchangeable biological products in BsUFA III. Examples here include the new Type 2a meeting, increased flexibility in requesting Biosimilar Initial Advisory meetings, and the same post-meeting follow-up opportunity as in PDUFA.

3. Dr. Marks, it goes without saying that CBER must be a strong, well-resourced partner to ensure safe and effective breakthrough therapies, such as cell and gene therapies, can benefit the patient. Congress established the breakthrough therapy designation in the Food and Drug Administration Safety and Innovation Act to ensure expedited review and approval of transformative therapies that are substantially improving the standard of care for a serious or life-threatening disease or condition.

a. Are you aware of any instances in which the FDA did not adhere to Agency regulations and guidance governing the breakthrough therapy program or regenerative medicine advanced therapy program, especially with respect to communication, transparency, and collaboration with the sponsor? Has FDA ever applied different standards of review for these therapies than for those cell and gene therapies that have received marketing authorization?

No, I am not aware of any instances in which FDA did not adhere to the regulations and guidance regarding breakthrough and RMAT programs. Regarding licensure, CBER has licensed three products with RMAT designation.

Because of the rapid growth in cell and gene therapy development, including the rapid growth in development programs for which we have granted breakthrough therapy designation and RMAT designation, it will be imperative that CBER be resourced appropriately. Without an investment in CBER, the benefits of these transformative products might not be realized in as timely a fashion as desired.

4. **Dr. Marks, Texas is a research leader in developing platforms for lifesaving gene therapies. Dr. Steven Gray and his team of researchers at the University of Texas (“UT”) Southwestern Medical Center in Dallas have received nearly five million dollars in grants from National Institute of Neurological Disorders and Stroke (“NINDS”) to develop gene therapy platforms for ultra-rare, genetic neurological disorders that are fatal in childhood, such as Rhett syndrome, giant axonal neuropathy (“GAN”), Tay Sachs disease, Sandhoff disease, Krabbe disease, and various types of Batten disease (CLN1, CLN7). According to the Massachusetts Institute of Technology, by 2030, FDA is likely to approve 30 gene therapies for rare genetic disorders, including this potentially life-saving medicine for GAN. A significant majority of these investigational gene therapies in clinical trials are for bleeding disorders, blood disorders, primary immunodeficiencies, metabolic disorders, neurodegenerative disorders, and muscle disorders for which there is significant unmet need, or the opportunity to greatly improve the current standard of care.**

- a. **What additional resources and authorities can be provided to CBER to ensure these transformative medical breakthroughs can save the lives of children with such devastating and potentially life-threatening conditions?**

A significant majority of the new resources negotiated for CBER in PDUFA VII are directed to the cell and gene therapy program. The new full-time equivalents (FTE) hired with these resources will be very important. However, we continue to see significant growth in the number of active cell and gene therapy development programs and FDA will continue to assess the resources needed to support sufficient staffing moving forward.

The Honorable Gus Bilirakis (R-FL)

1. **Dr. Marks, a Federal Register (FR) notice issued on January 3rd indicated several organizational changes across FDA and especially across CBER. While the notice provides an updated list of the organizational structures impacted — with CBER having the most changes, FDA has not disclosed details about staffing or leadership changes in the new areas. How would knowledge management and staffing or leadership changes be managed, and information be provided to sponsors for their applications including INDs?**

The Federal Register notice you refer to discusses reorganization of several FDA Centers. CBER's changes will help make the Center stronger and more effective. These include:

- streamlining and consolidating programs and operations to help support greater efficiency and better integration and alignment of work;
- minimizing organizational layers of review;
- ensuring process and policy consistency for quality assurance;
- positioning the Center to be better prepared to respond to developments and challenges in the industry they regulate and help drive innovation; and
- enhancing work life experience and professional development opportunities.

CBER information systems impacting knowledge management were updated to reflect organizational changes to ensure continuity of regulatory operations internally and with outside applicants.

As Offices adjust their structures, senior leaders are committed to ensuring that staff receive support and resources for a successful transition. The reorganization bolsters our ability to meet our mission and goals as outlined in CBER's [2021-2025 Strategic Plan](#).⁶

2. **Dr. Marks, the recent FR notice covering FDA reorganization also referenced the increase in applications for cell and gene therapy products and noted that the CBER reorganization will allow CBER to further advance RWE priorities for biologics. How do you specifically anticipate the reorganization – specifically the new Office of Biostatistics and Epidemiology– to further advance RWE priorities for biologics?**

Changes in CBER's Office of Biostatistics and Epidemiology (OBE), which will take on the new name Office of Biostatistics and Pharmacovigilance (OBPV) will help ensure that CBER's regulatory structures and processes are prepared to respond to innovation and development in the industry while upholding FDA's standards for safety and effectiveness for biological products. The changes will position CBER to advance real-world evidence priorities for biologics, with the newly created CBER Surveillance Program Staff which is able to drive continued innovation and successful implementation of FDA's real-world evidence framework. The new organizational structure will also better position CBER's Office of Tissues and Advanced Therapies (OTAT) to meet the increasing challenges and demands in this growing field, including continued growth in the Regenerative Medicine Advanced Therapy designation program established by the 21st Century Cures Act.

The Honorable Larry Bucshon, M.D. (R-IN)

1. **Aside from the “Four Part Harmony” approach to CMC communication and the CMC Readiness Pilot outlined in the PDUFA VII goals letter, are there other**

⁶ <https://www.fda.gov/media/81152/download>

strategies that the CDER and CBER intend to employ to improve communication on CMC issues?

The PDUFA VII goals letter includes a robust set of activities to improve FDA and industry communication on chemistry, manufacturing and control (CMC) issues. This includes the items noted in your question, along with staff training on CMC assessment processes associated with mid-cycle and late-cycle review meetings with the goal of ensuring that mid-cycle and late-cycle meeting expectations are met, including communicating the status of the NDA and BLA CMC assessment and any identified issues that would preclude approval.

In addition, CBER and CDER periodically examine communication approaches internally and formally (e.g., as part of communications assessment in previous PDUFA commitments). We update internal Manual of Policies and Procedures (MAPPs), Standard Operating Procedures and Policies (SOPPS), Q&As, and guidance on communication to reflect more efficient and effective processes and practices, share best practices and train staff on communication practices. Furthermore, information requests to applications, including those for CMC issues undergo review at various levels for content and clarity. Increases in staffing, and retention of existing staff can also facilitate communication by having trained and experienced subject matter experts to discuss technical topics.

The Honorable Earl L. “Buddy” Carter (R-GA)

1. **Dr. Marks, the biggest challenge faced by sponsors at FDA with respect to rare disease therapies are the lack of expertise on review teams with respect to the rare disease under review and the lack of knowledge and experience with rare diseases generally among different review divisions, which can lead to inconsistencies in sponsor experience and prolong the review process to the detriment of the patient. With the increase in BLAs submitted for cell and gene therapies in recent years and projected numbers for future years, from your perspective, what can be done at CBER to ensure each review division is well informed about each rare disease or condition under review, including phenotypes, rate of progression, and current standard of care? Do you believe it is feasible to conduct comprehensive training for all FDA product review staff on rare disease drug development?**

The Rare Diseases Team in CDER, Office of New Drugs (OND) coordinates with CBER, CDRH, and the Office of Orphan Product Development in the Office of the Commissioner (OOPD) to collaborate on annual staff training to share learnings and promote rare disease education regarding policy and review across the Agency. In addition, the Rare Diseases Team hosts quarterly seminars presented by internal and external experts to train and inform staff on timely and important aspects of rare disease drug development relevant to their work on rare disease applications. Trainings encompass both broad topics important across rare diseases (e.g. complex innovative design use in rare diseases) and innovative topics or policies (e.g. new scientific innovation in gene editing or new FDA guidance on the use of

real world data/evidence). Trainings include illustrative case studies, and are recorded and made available to FDA staff after the events to ensure access and availability.

OND has also established a new Rare Disease Drug Development Council comprised of leaders from across CDER's OND and from CDER's Office of Translational Sciences with expertise and experience in rare disease drug development to promote organizational cohesion across rare disease issues and drug development programs. CBER and other Centers also participate in this new council. These types of approaches will further enhance collaboration, consistency, and knowledge sharing between OND divisions and across CDER and FDA, while ensuring that each rare disease drug development program is evaluated by staff that have the disease-specific expertise needed to appropriately design and evaluate these programs.

CBER clinical review staff have diverse expertise covering a wide array of medical disciplines and most are knowledgeable about certain rare diseases within their respective disciplines. However, it is impossible for CBER clinical review staff to be knowledgeable from the outset on each of the more than 7,000 rare diseases that have been identified to date. Beside the many available cross-Agency training and information sharing opportunities about rare diseases described above, extensive online medical information resources are available to FDA review staff for obtaining the most up to date medical literature about specific rare diseases. Also, review staff have opportunities to hear first-hand from patients on their experiences in living with a specific rare disease during Patient Focused Drug Development meetings and Patient Listening Sessions, which are typically planned and held by or in collaboration with patient advocacy organizations. In addition to the programs previously noted in our response, CBER also provides monthly review management update training sessions to all staff. These trainings include refreshers on expedited review and development programs such as Fast Track, Breakthrough Therapy and Regenerative Medicine Advanced Therapy designation programs. Ensuring the appropriate application of these programs facilitates expeditious development of all eligible products including those for rare diseases. Through these various trainings and opportunities for information sharing, the effectiveness and efficiency of the review process is enhanced.

The Honorable John Joyce, M.D. (R-PA)

1. Will the FDA and IPMG commit to seeking stakeholder input prior proposing any substantial changes to the Clozapine and iPLEDGE REMS programs going forward?

While FDA can require manufacturers to implement elements under a risk evaluation and mitigation strategy (REMS) that are necessary for the safe use of the drug, such as periodic lab tests, certification of prescribers and pharmacies, or administration in a health care setting, the manufacturer determines the specific methods for implementing or operationalizing them. However, FDA encourages manufacturers responsible for implementing a REMS to seek stakeholder input from patient organizations and key professional organizations on the potential impact of REMS modifications to change third-

party vendors engaged by sponsors to aid in implementation of the strategies. We will continue to recommend sponsors take public input into account to achieve continuity and minimize disruption when undertaking changes that could impact REMS management.

2. Who will be responsible for the rollout of program adjustments in the future? And how will the FDA hold them accountable?

Manufacturers are responsible for implementing the REMS for products that are subject to REMS requirements and the rollout of any program adjustments (i.e., modifications) approved by FDA. For new products approved with a REMS, the REMS must be operational for the drug to be introduced into interstate commerce.

Based on recent experience with the unsatisfactory implementation of modifications to the Clozapine and iPLEDGE REMS, we have asked other manufacturers that are currently proposing REMS modifications that involve changes in third-party vendors engaged by manufacturers to aid in implementation and management of the strategy, to perform a Failure Mode and Effect Analysis (FMEA) before implementation. The FMEA would identify potential failures and a proposed contingency plan to address such circumstances. Our primary objectives are to support a smooth transition and to prevent interruptions in treatment for patients.

The Agency believes it is important to hold manufacturers accountable for the efficient and smooth implementation of a REMS and any subsequent modifications.

3. Will there be test runs for future program changes before rolling them out to the general public for physicians, pharmacists, and patients?

FDA does and will continue to recommend that, prior to informing the public of a new or modified REMS program, manufacturers seek stakeholder input and test any platforms that will be used.

4. Will stakeholders (professional organizations representing physicians and pharmacists) be provided a direct point of contact to work with and respond to questions and concerns in a timely manner?

Stakeholders with questions may contact the applicable product center (CBER, CDER, etc.) for that particular REMS.

Although FDA does not administer the product-specific REMS programs, FDA's Division of Drug Information (DDI) is a resource that is available for stakeholders and professional organizations if they have questions, concerns, or want to report an issue about a particular REMS program. This resource was a particularly helpful mechanism for FDA to hear about stakeholder concerns related to the implementation of modifications to third-party vendors in the Clozapine and iPLEDGE REMS.

5. How can we ensure physicians, pharmacists and patients across the country have full proper access to the Clozapine and the iPLEDGE program?

FDA strives to ensure stakeholders have access to all REMS programs without undue burden, including the Clozapine and iPLEDGE REMS. The goal is to maintain patient access while still preserving safe use of a drug.

Due to implementation issues, stakeholder access was impacted by the modifications to the iPLEDGE and Clozapine REMS. The modifications to these programs were necessary due to a change in the REMS vendor for both programs. The Clozapine REMS modification required stakeholders to recertify, and the iPLEDGE REMS required previous certified and enrolled stakeholders to update their log-in accounts. For both programs there were significant challenges with implementing these modifications. As the implementation of the changes to these REMS have begun to stabilize, stakeholders have been more successful in accessing the REMS programs, but the issues have not been entirely eliminated.

6. How can we ensure that the FDA and REMS do not reinstitute provisions of the REMS that risk interrupted treatment and result in harm to patients?

Since December 2021, FDA has been temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine.⁷ The Agency is analyzing metrics about the implementation of the Clozapine REMS and considering whether implementation issues affecting patient access to the medication have been addressed. Despite allowing additional time for stakeholders to enroll and certify, we have heard that some stakeholders will not certify in the REMS until it is absolutely necessary (e.g., once the enforcement discretion ends). Our highest priorities are continuity of care, patient access, and patient safety.

7. How can we ensure that the FDA does not reinstitute provisions of the REMS such as retroactive reporting of data that are not clinically useful?

The Clozapine REMS requires enrollment of all patients into a patient registry. The data collected through the registry, including repeated absolute neutrophil count (ANC), time to onset of neutropenia (if applicable), patient demographics, and patient health outcomes, can be used to evaluate the impact and frequency of the ANC monitoring. This information can be used to determine if changes are needed for labeling or the REMS to improve safety or reduce burden. While we believe this information will be very helpful, FDA does not intend to require retroactive reporting of ANC values and other information in the patient registry that was not collected during the period of enforcement discretion.

⁷ FDA is temporarily exercising enforcement discretion with respect to certain Clozapine REMS program requirements to ensure continuity of care for patients taking clozapine, available at <https://www.fda.gov/dmgs/drug-safety-and-availability/fda-temporarily-exercising-enforcement-discretion-respect-certain-clozapine-rems-program>.

Attachment—Additional Questions for the Record

**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022**

Lucy Vereshchagina, PhD., Vice President, Science and Regulatory Advocacy, Pharmaceutical Research and Manufacturers of America

The Honorable Gus Bilirakis (R-FL)

1. Dr. Vereshchagina, as Co-Chair of the Rare Disease Caucus I'm particularly interested in the work FDA and Congress can do to facilitate and improve regulatory pathways for rare disease R&D. Can you tell me more about the proposed pilot programs for Split Real Time Application Review in the PDUFA agreement and what that means for rare disease patients?

The Split Time Application Review (STAR) Pilot Programⁱ allows sponsors to split submissions of certain efficacy supplements, and FDA to split review of required sections of marketing applications. One of its goals is to shorten the time from the date of complete submission to the action date in order to expedite earlier patient access to novel uses of existing therapies that address an unmet medical need. The STAR program will expedite patient access to novel uses for existing therapies by supporting initiation of review earlier than would otherwise occur and therefore allowing earlier approval for qualified efficacy supplements. This program, beginning in fiscal year (FY) 2023, will apply across all therapeutic areas and review disciplines for applications that meet specific criteria.

As many rare diseases represent areas of unmet medical need, PhRMA hopes that sponsors developing drugs and biologics for new rare disease indications will be utilizing this program and that rare disease patients will benefit from the expedited drug review process.

In order to increase transparency and opportunities for public engagement, the Food and Drug Administration (FDA or Agency) will develop a public-facing webpage outlining detailed criteria for potential acceptance and participation in the STAR program. FDA will also conduct an interim assessment that includes internal activities related to STAR by the end of FY 2025. A public workshop will be held to discuss the potential value and feasibility of expanding the pilot program to select New Drug Applications (NDAs) for New Molecular Entities (NMEs) and Biologics License Applications (BLAs) and solicit feedback on experiences with the pilot program from industry stakeholders. FDA also committed to training review staff on STAR processes and providing a publicly available report summarizing training activities conducted.

PhRMA would also like to highlight additional PDUFA VII provisions that will advance and facilitate the development and timely approval of drugs and biologics for rare diseases, including rare diseases in children. Importantly, FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) have committed to continuing the integration of rare disease staff into review divisions to ensure rare disease expertise is optimized throughout the review process.

PDUFA VII also includes the Rare Disease Endpoint Advancement (RDEA) pilot program to develop novel endpoints for rare disease clinical trials. The lack of regulatory precedent, small trial populations, and/or limited understanding of disease natural history associated with rare diseases creates unique challenges when determining the appropriate efficacy endpoint(s) for clinical trials intended to evaluate the effectiveness of rare disease therapies. Though difficult to establish, well-developed efficacy endpoints, especially those that could apply to other rare diseases with similar manifestations, drive the general advancement of rare disease drug development. In addition to challenges associated with developing endpoints that appropriately capture key signs and symptoms of a rare disease and directly measure how patients feel, function, or survive, surrogate endpoint development is also challenging in diseases with slow progression, small patient populations, or other challenges commonly associated with drug development in rare diseases.

Current mechanisms for sponsors of rare disease drug development programs to collaborate with FDA are not structured to provide repeated, intensive interactions with the Agency. The Pilot will offer additional engagement opportunities between FDA and the sponsor to support the advancement of rare disease treatments. In addition, FDA will hold public workshops to discuss various topics relevant to endpoint development for rare diseases. To promote innovation and evolving science, novel endpoints developed through the RDEA pilot may be presented by FDA, such as in guidance documents, on a public-facing website, or at public workshops as case studies. FDA staff capacity will also be expanded to enable and facilitate appropriate development and use of these types of novel endpoints. This staff will support the complex and intensive review work necessary to evaluate novel endpoint development with a focus on the challenges of trial designs utilizing small populations.

2. Dr. Vereshchagina, can you provide the number of new products the user fee agreements have helped bring to market overall, and how many have specifically been brought under Accelerated Approval?

Since 1992 when the program was first enacted, PDUFA has provided more timely patient access to more than 1,700 new drugs and biologics including treatments for cancer, rare diseases, cardiovascular, neurological, and infectious diseases. Before PDUFA, it often took FDA more than two years to review new medicines. In 2021, the Center for Drug Evaluation approved 50 novel drugs. 86% were approved on the first cycle. 76% were approved in the United States before any other country. 52% were for rare or orphan diseases. 54% were First-in-Class.ⁱⁱ

Medicines approved under accelerated approval address unmet medical needs for serious and life-threatening diseases and conditions and meet FDA's high standards for safety and effectiveness. This pathway has provided timely access to hundreds of treatments for HIV/AIDS, cancers and rare diseases, leading to better health outcomes for millions of patients. Since the inception of accelerated approval in the early 1990s, over 250 new drugs and biologics to treat serious or life-threatening illnesses have been approved through the accelerated approval pathway. From 1992 through about 2010, accelerated approval was primarily used for drugs indicated for the treatment of HIV (39.7% of approvals), cancers (35.6% of approvals) and other rare disease treatments and specialty drugs (24.7% of approvals). In 2021, CDER approved 14 of the 50 novel drugs (28%) under Accelerated Approval.ⁱⁱⁱ

The upcoming PDUFA VII efforts are aimed at modernizing the U.S. regulatory and drug development paradigm and improving efficiencies in drug review, including for post-marketing requirements (including those for accelerated approval drugs). For example, FDA will update their review processes to provide timelier discussions between sponsors and the Agency to help ensure earlier agreement on post-marketing requirements, including for drugs and biologics approved under the accelerated approval pathway.

ⁱ Real Time Oncology Review (RTOR) is separate from the STAR pilot program. Sponsors developing oncology products can still utilize the RTOR program.

ⁱⁱ FDA New Drug Therapy Approvals 2021. Available at <https://www.fda.gov/media/155227/download>

ⁱⁱⁱ FDA New Drug Therapy Approvals 2021. Available at <https://www.fda.gov/media/155227/download>

Attachment—Additional Questions for the Record

**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022**

Cartier Esham, Ph.D., Chief Scientific Officer, Executive Vice President, Emerging Companies,
Biotechnology Innovation Organization

The Honorable Lisa Blunt Rochester (D-DE)

- 1. What more can the industry do to expand clinical trial diversity, and what more can the FDA do to support biotechnology companies, academic institutions, and related organizations seeking to increase clinical trial diversity?**

Response:

To drive the industry's efforts to create a more expansive, inclusive, and sustainable clinical development ecosystem, BIO along with our Industry members developed a policy strategy to focus on the removal of regulatory barriers and enhance and develop lagging data sources and infrastructure. We acknowledge that even with improvements to these technical components, many barriers to inclusive clinical trial participations still exist, including language and health literacy differences and historical mistrust of clinical ethics. BIO is committed to working with stakeholders across the spectrum to address these critical components.

The barriers to a clinical development paradigm that are more effective, efficient, and patient centric within FDAs purview are:

1. **Lack of reliable data sources** and alignment on how to set representative targets- U.S. demographic data is incomplete or lacking for many disease areas. This leads to poorly or inaccurately informed enrollment targets and actions plans during drug development. While FDA regulations require sponsors to present a summary of safety and effectiveness data by demographic subgroups their trials, it is difficult to compare this data to epidemiology data to understand whether enrollment targets are representative of the disease population. Additionally, the FDA and industry need to discuss and establish acceptable methodologies to set enrollment targets that are representative of the disease population as we work to improve data sources.
2. **Lack of certainty regarding clinical trial parameters** - There is lack information for drug sponsors regarding how the FDA views clinical trial parameters that are essential to patient recruitment, such as how to support and establish demographic enrollment targets and inclusion/exclusion criteria.

3. **Lack of certainty regarding innovative clinical trial designs.** Clinical trial designs with regulatory certainty are often geographically centralized around academic medical centers and burdensome to participate in (multiple mandatory visits to the clinic). This makes it difficult to recruit individuals from different geographic localities and individuals who aren't economically able to travel or take time off from a job. Modern trial designs that embrace 21st Century technologies (i.e., use of digital technologies, decentralized clinical trials, RWE) that have been shown to be successful in facilitating trials and driving diverse enrollment during the COVID-19 pandemic¹ lack regulatory direction and certainty from the FDA.

BIO appreciates FDA's ongoing efforts to delineate clinical trial diversity expectations, including the April 2022 *Draft Guidance Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials*. We look forward to working with FDA to ensure that this and future guidance documents adequately address the needs of patients, industry, and other relevant stakeholders. However, there are other potential solutions that would support FDA's ongoing efforts that are outlined below.

Potential Solution to support FDA's ongoing efforts

- ***Create and Share Reliable Epidemiological Data Sources***
Modeled from Patient Informed Drug Development meetings and information sharing, FDA should hold public meetings with comment periods on followed by issuing guidance on:
 - How and when drug sponsors should collect and present disease prevalence and demographic data, the methodologies sponsors should use to conduct diversity assessments, and the criteria FDA considers when accepting various epidemiological data sources data in Investigational New Drugs Application (INDs).
 - How to create more reliable data sources for more diseases, and make data readily and publicly available to all sponsors.
- ***Create Certainty in Clinical Trial Parameters***
Require FDA to establish an FDA-Sponsor Diversity Engagement Strategy Framework and plan for pivotal trials:
 - The Goals of the Diversity Engagement Strategy would be to enable timely engagement for sponsors and FDA to meet and discuss demographic and/or disease prevalence data and target enrollment during drug development, for approval and any post-approval commitments for continued collection of such data.
- ***Develop Robust Guidance and internal process documents***

¹ <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789002>

While not legally binding, guidance documents serve as de facto parameters for FDAs expectations which drug sponsors closely follow. FDA, after holding public meetings with comment periods should issue guidance to address the following issues

- The type, timing, and requirements for meetings between FDA and drug sponsors to engage on developing demographic and/or disease prevalence targets for investigational new drug applications (INDs), New Molecular Entity New Drug Applications/Biologics Licensing Application (NME NDAs/BLAs).
 - Criteria and rationale for establishing clinical trial demographic and/or disease prevalence targets in INDs and in NME NDAs/BLAs needed to support FDA approval, including special considerations for small or genetically targeted patient populations.
 - Criteria and rationale for post marketing commitments for demographic and disease prevalence data including utilization of RWD/RWE.
 - Approaches for inclusion and exclusion criteria, study/trial designs, clinical endpoints, biomarker selection, study analysis to better enable inclusion of underrepresented communities.
 - Reporting requirements and inclusion of demographic and disease prevalence data in prescription drug labeling and processes for updating information.
 - Develop internal process document (SOPP, MAPPs, templates) to train and educate review teams on the criteria and rationale established above.
- ***Advance Innovative Trial Design and Digital Health Technologies***
Providing sponsors with clarity regarding the FDAs view of decentralized trials, use of RWD/RWE, use of digital health tools to collect endpoints, such as remote monitoring devices, cell phones, smart watches, and non-traditional clinical trial locations will help drive the uptake of these tools. While not legally binding, guidance documents serve as de facto parameters for FDAs expectations which drug sponsors closely follow. FDA, after holding public meetings with comment periods should issue guidance to address the following issues
 - The use of DHTs in traditional and decentralized trials, including addressing the validation of measurements made by DHTs, the use of DHTs to measure existing endpoints, and usability considerations by diverse populations.
 - Approaches for generating real world evidence capturing diverse communities that can meet regulatory requirements in support of labeling.

Other Policy Solutions for Consideration

- ***Communication plan for information sharing***
Require FDA to reform and expand on Drug Trials
 - Require transparent tracking of demographics in premarket clinical trials of drugs and reported as part of the Drug Trials Snapshot at the time of FDA approval.

- Enable sponsors to submit contextual information for individual snapshots that can be updated as information evolves

Build a more Expansive, Inclusive, and Sustainable Clinical Trial Network Infrastructure

- Require that HHS conduct a series of public roundtable discussions between NIH, FDA, CDC, community organizations, Industry, and CROs to meet regularly to discuss and report on advances in diverse recruitment and develop new strategies in a collaborative way. Potential topics for roundtable:
 - Establishing a publicly available database of active clinical trialists identifiable by facility and area of experience including where should it be housed, reporting requirements by medical facility and/or clinical trialists.
 - Establishing clinical trialists training programs and mentoring networks for investigators, trialists and facilities serving underrepresented communities.
 - Establishing a publicly available database of community engagement organizations supported by NIH
- No later than 90 days after each public roundtable discussion, HHS should make available on their website a report and recommendations on the topics discussed at the roundtable discussion.
- No later than 180 days after each public roundtable discussion, HHS should make available on their website an implementation plan and actionable activities on the topics discussed at the roundtable discussion.
- Require HHS to establish or leverage existing programs for a federally funded clinical trial investigator fellowship pilot program for women, LGBTQIA+, racial and ethnic minorities to help increase representation of underrepresented population.
- ***Diversity and Inclusion for workforce development***
Require FDA and NIH to improve transparency around hiring, retention and promotion practices within their organizational leadership and scientific workforce.
 - Establish clear objectives to diversity organizational leadership and scientific workforce.
 - Provide regular reports to Congress on metrics around hiring, retention and promotion of diverse leadership and scientific workforce.

The Honorable Gus Bilirakis (R-FL)

1. As Co-Chair of the Rare Disease Caucus, I'm particularly interested in the work FDA and Congress can do to facilitate and improve regulatory pathways for rare disease R&D. Can you tell me more about the proposed pilot programs for Split Real Time Application Review in the PDUFA agreement and what that means for rare disease patients? Dr. Esham, can you elaborate on this and explain what this means for companies conducting clinical trials for these rare disease treatments and cures?

Response:

BIO appreciates the opportunity to provide additional comments about strategies to bring medications to patients who need them as safely and quickly as possible, especially for those suffering from rare diseases who often lack other treatment options. As noted in my testimony, there are at least 7,000 known rare diseases collectively impacting over 25 million Americans with new rare diseases identified each year. The PDUFA VII Commitment Letter contains several provisions that will build upon the efforts of previous agreements to address this critical issue that remains a priority of BIO and our member companies.

The Split Real Time Application Review (STAR) pilot program aims to shorten review timelines for certain drug and biological products that are intended to treat serious conditions with unmet medical needs. It builds on innovative review concepts that have proven successful for FDA's Real Time Oncology Review (RTOR) program by expanding them to all disease areas outside of oncology, enabling more timely reviews and availability of these medicines to vulnerable patient populations. More specifically, STAR's scope includes efficacy supplements across all therapeutic areas and review disciplines that meet certain criteria described in the Commitment Letter. For applications accepted into the STAR pilot program, review activities and workload will be streamlined for both FDA and sponsors by allowing the sponsor to submit an application in two parts rather than the traditional single part, enabling FDA to begin review of key application components as much as 2-3 months earlier than usual. The goal for applications reviewed under STAR is to allow FDA to provide a regulatory decision at least one month earlier than the priority 6-month PDUFA action date.

Rare disease patients in particular stand to benefit from STAR significantly due to the pilot program's eligibility criteria. The medical product must have clinical evidence indicating that it could demonstrate substantial and quantifiable improvement on a clinically relevant endpoint compared to currently available therapies. Also, the product must be intended to treat a serious condition with an unmet medical need. As a result of these criteria, products reviewed under STAR could directly benefit those suffering from rare diseases by expediting patient access to innovative and novel uses for existing therapies by allowing FDA to initiate review earlier than would otherwise occur, enabling earlier approval of these products. For these patients without other viable options, getting treatments potentially months earlier can be the difference between relief, disability, or even death.

Companies with applications accepted into STAR who are conducting clinical trials for these rare disease treatments and cures benefit directly through increased workload and pipeline management efficiency. The requirements for each of the two submissions, as clearly defined in the Commitment Letter, allow the sponsor to prioritize clinical data collection, analysis, and submission in a way that provides FDA review teams with information essential to beginning their evaluation while the company continues to compile the second submission requirements. This could prevent workload and resource-related delays in the submission of applications that are not only the focus of STAR but also for other products in the company's pipeline with potential to help more patients. With more regulatory flexibility, the company can optimize resource allocation to bring as many new treatments to FDA for review as possible.

The Commitment Letter also includes training requirements for FDA staff to ensure review teams are prepared to execute on earlier and faster evaluations as soon as the pilot program begins. In addition, FDA will conduct a public workshop by the end of Q2 in FY 2026 to discuss the potential value and feasibility of expanding the scope of the pilot program from efficacy supplements only to certain new drugs and biologics, potentially increasing the impact of the program to even more patients, including those suffering from rare diseases.

With respect to advancing science related to rare disease treatment generally, the STAR pilot program will be well-complemented by another pilot program described in the Commitment Letter, the Rare Disease Endpoint Advancement (RDEA) pilot program. Because rare diseases have limited or no treatment options and lack well-established regulatory precedents, the development and review of these medicines introduces additional challenges that must be overcome to deliver new therapies to patients who need them. Key among these challenges is reaching agreement with regulators about determining the appropriate efficacy endpoints to support approval of innovative medicines for rare diseases. The current mechanisms for companies with rare disease treatments in their pipeline to collaborate with FDA have not consistently provided avenues for much needed discussions about these unique issues, which can cause delays in the development and availability of medicines to these patients who often lack options. The RDEA pilot program will provide avenues for focused engagement opportunities that will serve to advance and share learnings and enable more efficient drug development and review process for all rare disease medicines.

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Attachment—Additional Questions for the Record

**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022**

Juliana M. Reed, President, Biosimilars Forum

The Honorable Richard Hudson (R-NC)

1. In your testimony and throughout the hearing, you and others highlighted the impact the COVID-19 pandemic has had on biosimilars and patient access, specifically citing FDA's growing backlog of delayed foreign inspections. As you also noted, FDA's own data has shown a steep decrease in FDA's ability to meet biosimilar user fee goal dates, with on-time actions dropping significantly lower than those for other drug applications. Given the ability for biosimilars to lower the cost of some of the most expensive medicines, please explain in detail how these inspection delays have impacted the biosimilar marketplace and patient access. In addition, please explain any and all specific policies or actions the Biosimilars Forum believes are necessary to successfully address the growing backlog.

Answer: Not only has the COVID-19 related inspectional backlog had a significant impact on biosimilars but also it appears that biosimilars have been more adversely affected by these pandemic-related inspectional issues than other product areas. As reflected in my February 3, 2022 testimony, the percentage of on-time actions for biosimilars is far from the negotiated targets and has been markedly worse than for other user fee programs. FDA generally does not disclose its reasons for missing the action date for a particular application. However, FDA has explained that it will defer action (*i.e.*, miss the goal date) for an application if an inspection is deemed necessary but, in the Agency's view, cannot be completed due to factors including travel restrictions and the application otherwise meets the requirements for approval. Without FDA approval, these critical medicines cannot be marketed, undercutting the Agency's commitment to improving access through increased competition. Additionally, to reiterate from my testimony, biosimilar inspections are not considered by the Agency to be "mission critical" and thus are not being prioritized.

The Forum continues to strongly support efforts to advance a robust biosimilars program, with the corresponding benefit of increased patient access to high quality, safe, effective, and affordable therapies. We believe that there are a number of specific policy tools and actions that could help address the growing inspections backlog. For example, FDA could be authorized to leverage existing tools to enable the Agency to use Remote Interactive Evaluations (RIEs) or records requests pursuant to section 704(a) of the FD&C Act to clear Official Action Indicated and p-OAI facilities. In addition to increasing the availability of alternatives to on-site

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inspections, more robust reporting requirements, such as posting real time information on the number of biosimilar facilities inspected during the prior month and the number scheduled for inspection the following month, could enhance transparency and accountability. And, recognizing that on-site inspections may be needed in certain circumstances, the Agency could coordinate with the State Department (through a statutory directive or other mechanism) to ease inspector access to foreign countries.

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**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022**

David Gaugh, Senior Vice President, Sciences and Regulatory Affairs, Association for
Accessible Medicines

The Honorable Gus Bilirakis (R-FL)

1. Mr. Gaugh, your testimony specifically calls out the importance of competition in the drug marketplace, and how there is significant evidence of prices decreasing, in some cases by nearly 80 percent when four or more generics enter the market. FDA also mentions that the last GDUFA legislation had required Priority Review to become available for applications for generic drugs with limited competition, as well as for generic drugs in shortage. These provisions were a direct result of legislation I co-led with Rep. Schrader, the Lowering Drug Costs through Competition Act. This bill also created the Competitive Generic Therapy program, and I was pleased to see this past fall that FDA has approved over 100 generic drug applications with Competitive Generic Therapy designation. This means we are starting to see more competition in the marketplace, which will help alleviate prices. That's why it is critical we have a predictable review process at FDA to ensure smooth and quick approvals, particularly when we are dealing with complex generics. Can you explain how this next GDUFA commitment letter will build upon the successes of these programs for generics with little to no competition in the market, and can you explain how we can continue to ensure a transparent process for drug innovators?

The Competitive Generic Therapy (CGT) designation was established under the *FDA Reauthorization Act of 2017* (FDARA) to provide new incentives for generic manufacturers to develop and commercialize medicines in areas where there is inadequate competition. The CGT listed drugs are generally brand-name drugs that lack adequate competition despite the expiration of all patents and exclusivities that would otherwise block generic competition. Therefore, for various reasons, there is inadequate generic competition, which results in less access to more affordable medicines. The CGT pathway has been remarkably successful at generating competition in areas where it was previously lacking. Since 2018, FDA has approved 130 CGT products. AAM applauds your and Representative Schrader's leadership in developing this important program.

While there is nothing in GDUFA III specific to CGT products, there are several enhancements in the Commitment Letter that will also be helpful in facilitating the continued development of CGTs. For example, the "imminent action" enhancement will allow FDA to extend a goal date

by 60-days without triggering a new review cycle if an approval or tentative approval of the ANDA Application (including a CGT Application) will occur within these 60-days. This enhancement will help mitigate the need for additional review cycles, which could unnecessarily delay ANDA Applications (including CGT Applications) over imminently resolvable issues. CGTs that are complex generic medicines will also benefit from GDUFA III enhancements in the Commitment Letter, as FDA will be issuing more product-specific guidances for complex medicines, which will increase predictability for developers by creating more transparency over FDA's product development expectations.

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**Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022**

Reshma Ramachandran, M.D., Chair, Doctors for America FDA Task Force, Physician-Fellow,
Yale National Clinician Scholars Program, Yale School of Medicine

The Honorable Michael C. Burgess, M.D. (R-TX)

Response: Thank you for these thoughtful questions regarding the use of real-world evidence (RWE) in the regulatory review process. Please find my responses below to the questions posed. I would also be happy to meet to discuss the questions and responses further.

- 1. According to your testimony you seem to imply that there is an intent to replace clinical trials with real-world evidence (RWE). To my knowledge, RWE has been used very successfully to supplement data from clinical trials, and the goals in PDUFA VII are aimed at trying to improve how we can use RWE and to evaluate the potential for new use cases. Is that not the case?**

Real-world evidence (RWE), which is defined by the FDA as “information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications”, has helped inform regulatory decision-making, complementing robust clinical trials.¹ For instance, RWE has been utilized in capturing safety signals for new drugs and medical devices that would not have otherwise been captured until these products were made available in clinical practice to a larger population of patients and for a longer duration than that of clinical trials. FDA’s Sentinel Initiative is an example of such a platform that harnesses and harmonizes real-world data (RWD) through EHRs, claims, and other data sources from insurers and healthcare delivery systems.²

Moreover, RWE has been used to inform supplemental indication approvals for medical products already on the market. For instance, FDA approved additional indications for transcatheter heart valves with evidentiary support from data collected in a postmarket valve registry that was created as a result of a Medicare coverage decision.³ Just last year, FDA for the very first time utilized real-world evidence to approve Prograf (tacrolimus) in combination with other immunosuppressant medications for the supplemental indication of preventing organ rejection in adult and pediatric patients receiving lung transplantation.⁴ For this approval, FDA used robust RWD sources including U.S. Scientific Registry of Transplant Recipients (SRTR), which has data collected on all lung transplants in the country. This was further augmented by a trusted data source on

mortality from the Social Security Administration's Death Master File. FDA worked closely with the manufacturer to design a rigorous, non-interventional trial to demonstrate a significant improvement in outcomes among lung transplant patients who received Prograf as part of the immunosuppressant regimen compared to those who did not. It should be noted that FDA also considered randomized-controlled trials of the drug in other solid organ transplant patients as confirmatory evidence as well as other published clinical trial evidence.

While there is growing evidence of the potential capability of RWE to be used complementary to clinical trials in the regulatory review process, proposals have emerged to more hastily allow for RWE to replace clinical trials, particularly for supplemental indications and fulfillment of postapproval study requirements. Such proposals include:

- H.R. 6996, the *Accelerating Access for Patients Act* would allow for sponsor to utilize "clinical evidence, patient registries, or other sources of real-world evidence" to fulfill postapproval study requirements (Sec(2)(a)(2)(A)). The legislation also asks FDA to issue a report within 180 days of passage around the current use of RWE in supporting or fulfilling postapproval confirmatory study requirements (Sec(2)(a)(6)(A) and (B)).⁵
- H.R. 6000, *Cures 2.0* would allow RWE to be submitted as confirmatory evidence of clinical benefit to fulfill postapproval study requirements (Title III – Section 309).⁶
- Within FDA's PDUFA VII Commitment Letter,⁷ FDA committed to establishing a pilot "Advancing RWE Program" that would identify approaches for generating RWE in "support of labeling for effectiveness or for meeting postapproval study requirements." Under this program, FDA will solicit sponsors through a competitive application process to pilot RWE approaches that can feasibly be used as part of the regulatory review process. Such an approach does have the potential in providing FDA with further information on the advantages and limitations of RWE in making regulatory review decisions, including for new indications and fulfillment of postapproval studies meant to confirm clinical benefit. This could enable necessary improvements to RWD sources in a stepwise manner unlike the aforementioned legislative proposals that would pre-empt such improvements from being made to RWD sources.

My colleagues examined whether it would be feasible to use such RWD sources in the form of EHR or claims data to emulate FDA-required postapproval confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.⁸ Of the 50 confirmatory trials required by the FDA for these drugs, none could be feasibly emulated using currently available RWE sources in terms of medical claims or structured electronic health record data. The findings of this study suggests that currently available RWD sources and observational methods are unlikely to replace postapproval confirmatory trial requirements as has been proposed in legislative proposals. Moreover, my colleagues also examined whether any US-based clinical trials for novel drugs published in high-impact medical journals could be feasibly replicated using similar RWD sources, finding that only 15% could.⁹ Thus, while RWE has demonstrated promise in complementing clinical trial data for medical products, there has not been demonstrated evidence to suggest that

RWE can be used to replace clinical trials and that it may be premature to codify such use under legislation.

a. Do you have any recommendations on how to improve the quality and accuracy of the data received from electronic health records and claims?

Electronic health record (EHR) and claims data were not designed for the purposes of regulatory review, which lends to their limitations in being utilized for this purpose, despite having advantages compared to more costly, complex, and lengthy data collection methods through clinical trials. On one hand, EHR data in its ideal form does include detailed clinical information about patients including demographic information as well as other underlying conditions and prescribed or administered treatments. However, even these advantages may be limited if there is uneven data quality or limited inter-operability across different health systems where patients may be seeking care (e.g. for instance, several of my patients seek care through the Yale New Health System as well as the Veterans Health Administration, which have two completely different EHRs and no mechanism for inter-operability). Additionally, should patients seek care at another health system or provider without inter-operability, longitudinal data around efficacy or safety of a medical product may also be limited.

Moreover, there may be a lag period in certain data elements including other medical conditions or treatments that a patient may be receiving. This is critical for understanding whether the treatment effect seen in an RWE study is attributable to a drug or device product. Other unmeasured confounders – that is, something that could be influencing the patients receiving the product of interest and outcomes of interest but not reflected within the available data – could also be present. Additionally, EHRs very rarely include data on patient-reported outcomes as the data collected is by the clinician or provider such that key information regarding whether a drug or device affected their quality of life, symptoms such as pain or fatigue, or other health behaviors will likely not be reflected in this data source.

Claims data also have similar, potential advantages (provided that patients remain in the same health system or with the same payer over time) in that data collection and abstraction can be fairly simple and efficient. As coding standards even across health systems may be widely accepted, claims data would be fairly consistent. However, claims data do not include detailed clinical information as in EHRs and within such data, there may be difficulty in differentiating patient comorbidities from complications. Additionally, patients may move across health insurers making it difficult to collect longitudinal data for follow-up. There also may be a time lag in the data due to coding typically being completed after the clinical care encounter.

In a recent study conducted by my colleagues, they sought to use RWE in the form of EHR and claims data to emulate a randomized-controlled trial comparing the cardiovascular risk of two prostate cancer drugs.¹⁰ They found that only a quarter of real-world patients using the examined drugs met the randomized controlled trial's narrow inclusion and exclusion criteria. They were also not able to use RWE to precisely emulate the endpoints examined within the randomized-controlled trial. The authors did highlight a few key considerations for enhancing EHRs and claims data in such RWE studies including:

- the need for adequate observational data to emulate clinical trial enrollment criteria and for the evaluation of endpoints, as specific endpoints for this RWE study such as mortality due to cancer or whether cardiovascular events were fatal or not were unable to be determined using claims data;
- consideration of whether data allows for adequate follow-up and whether enrollment dates are available within the data source to ensure a sufficient follow-up period, noting that EHRs would not have such dates; and
- the need for comparison to clinical trials to determine whether patient or provider behaviors or other confounding variables may have contributed to the observed findings.

FDA recently issued draft guidance in late October on “Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products.” With Drs. Joseph S. Ross (Professor of Medicine and Public Health) and Sanket S. Dhruva (Assistant Professor of Cardiology, University of California, San Francisco), we submitted comments on how such guidance could be further strengthened to ensure the integrity of the data towards informing regulatory decisions.¹¹ Some of these recommendations include:

- **mandatory registration and results reporting of all RWD-based studies of FDA-regulated medical products with prespecification** of data sources, all endpoints, statistical analysis plan, and public reporting of results from all analyses either to coincide with submission for publication or within 6 months of study completion – such registration and results reporting through *ClinicalTrials.gov* are already statutorily mandated for clinical trials under the Food and Drug Administration Amendments Act of 2007, which can be further expanded to include RWE studies;
- **sponsors of RWE studies should submit protocols and statistical analysis plans to FDA before initiating the study** to allow the agency to ensure appropriateness of endpoints, availability of study data within the prespecified RWD sources that would be used, and methods to mitigate the effect of unmeasured confounders that could obscure the observed study findings;
- **inter-operability of RWD sources including EHRs across health systems and organizations** to limit the presence of missing data including for follow-up and overcounting the same patients who may be seen across different health systems as well as to allow for longitudinal data for

adequate follow-up of patients who may move their care to a different health system after a period of time;

- **RWD sources such as EHRs should contain adequate numbers of patients with adequate follow-up for outcomes of interest**, but such that follow-up would entail consistent measurement of the outcomes of interest (one example we included as part of our comments to FDA was that of a patient receiving a drug for cardiovascular disease with follow-up at one year for safety and efficacy; it is possible that the EHR would show that the patient sought follow-up care at one year, but at a non-cardiovascular or other relevant clinic, which should not be considered as adequate follow-up);
- **RWD should include accurate and updated information of both prescription as well as non-prescription drugs and those are not reimbursed by payers** that if either not updated or included, would confound any observed findings;
- **RWD sources should account for missing data often not captured within EHR or claims data** including tests or treatments either not ordered, ordered but not conducted/received, conducted/received but not reflected in the data sources, or where data is just not available; and
- **validation of outcomes collected and abstracted from RWD sources, particularly proxy measures that meant to be reflective of endpoints collected in clinical trials** as there may be heterogeneity in how these proxy measures are collected.

Ideally, Congress should mandate medical product sponsors to register RWE studies including their protocols onto a public database such as ClinicalTrials.gov (or other publicly accessible database) as they are required to do with clinical trials. Congress should also mandate sponsors to report RWE study results onto ClinicalTrials.gov (or other publicly accessible database) in a timely manner as described above. FDA should also be given enforcement authority to ensure compliance with registration and reporting as they have with clinical trials. Sponsors should also be required to collaborate with the FDA in establishing their RWE study protocols to ensure oversight and integrity of the RWD sources, collection, and abstraction.

b. How can we be encouraging better data collection at the point of care with regulatory decision-making in mind?

Infrastructure investment to allow for better and sufficient data collection at the point of care will be needed. As mentioned earlier, EHRs, which would be the primary source of point-of-care clinical care information as well as claims data were not designed for the purposes of regulatory decision-making or clinical research. Enhanced data collection at the point of care must also be balanced with time constraints for clinicians and other providers as well as patients in making clinical care decisions. FDA is exploring the use of artificial intelligence and machine learning towards this goal and to leverage other unstructured sources of

data. However, engagement of patients, clinicians, and other providers to examine the real-world impacts of data collection methods and their impact on clinical care will be needed. These stakeholders can provide valuable insight in how to seamlessly integrate the accurate collection of data elements necessary for a robust RWE study at the point of care without increasing their resource burden in doing so.

As a first step, requiring that sponsors submit their protocols to FDA for RWE studies ahead of initiating them would allow the agency to examine the RWD sources to determine specific considerations for data collection including the need for additional or substitute proxy measures. Ideal data sources would not only include clinician-entered clinical data, but also those that are patient-reported and patient-generated. For collecting such data from patients in an efficient manner, opportunities to engage patients outside of the clinical care setting are being piloted including through mobile applications from health systems and organizations and tele-health. However, validation of such data by the FDA is necessary to ensure an accurate association with meaningful clinical outcomes. Quality control measures must also be in place to ensure data validity. Finally, training of clinicians and other providers to ensure consistency and accuracy of data collection as well as to prevent against heterogeneity in data reporting.

References:

1. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence — What Is It and What Can It Tell Us? *New England Journal of Medicine*. 2016;375(23):2293-2297. doi:10.1056/NEJMsbl609216
2. Commissioner O of the. FDA's Sentinel Initiative - Background. *FDA*. Published online February 4, 2022. Accessed April 20, 2022. <https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background>
3. Dhruva SS, Ross JS, Desai NR. Real-World Evidence: Promise and Peril For Medical Product Evaluation. *P T*. 2018;43(8):464-472.
4. Research C for DE and. FDA approves new use of transplant drug based on real-world evidence. *FDA*. Published online September 30, 2021. Accessed April 20, 2022. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence>
5. Rodgers CM. *Accelerating Access for Patients Act of 2022*. Accessed March 15, 2022. <https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BILLS-117hr6996ih.pdf>
6. DeGette D, Upton F. *Discussion Draft: Cures 2.0 Act.*; 2021:127. https://degette.house.gov/sites/degette.house.gov/files/Cures%202.0_DISCUSSION%20DRAFT.pdf

7. Food and Drug Administration. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Published online September 28, 2021. Accessed October 5, 2021. <https://www.fda.gov/media/151712/download>
8. Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. *JAMA Network Open*. 2021;4(11):e2133667. doi:10.1001/jamanetworkopen.2021.33667
9. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. *JAMA Network Open*. 2019;2(10):e1912869. doi:10.1001/jamanetworkopen.2019.12869
10. Wallach JD, Deng Y, McCoy RG, et al. Real-world Cardiovascular Outcomes Associated With Degarelix vs Leuprolide for Prostate Cancer Treatment. *JAMA Network Open*. 2021;4(10):e2130587. doi:10.1001/jamanetworkopen.2021.30587
11. Dhruva SS, Ramachandran R, Ross JS. Public Comments on Draft Guidance (FDA-2020-D-2307), “Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products.” Published November 21, 2021. Accessed April 20, 2022. <https://www.regulations.gov/comment/FDA-2020-D-2307-0016>