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THE FUTURE OF MEDICINE:

LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

THURSDAY, MARCH 17, 2022

House of Representatives,

Subcommittee on Health,

Committee on Energy and Commerce,

Washington, D.C.

The subcommittee met, pursuant to call, at 10:34 a.m. in the John D. Dingell Room, 2123 of the Rayburn House Office Building, Hon. Anna Eshoo [chairwoman of the subcommittee], presiding.

Present: Representatives Eshoo, Butterfield, Matsui, Castor, Sarbanes, Welch, Schrader, Cardenas, Ruiz, Dingell, Kuster, Kelly, Baragan, Blunt Rochester, Craig, Schrier, Trahan, Fletcher, Pallone (ex officio); Guthrie, Upton, Griffith, Bilirakis, Long, Bucshon, Hudson, Carter, Dunn, Curtis, Crenshaw, Joyce, and Rodgers (ex officio).

Staff Present: Lydia Abma, Fellow; Vincent Amatrudo, FDA Detailee; Jacquelyn Bolen, Health Counsel; Waverly

Gordon, Deputy Staff Director and General Counsel; Tiffany Guarascio, Staff Director; Stephen Holland, Senior Health Counsel; Zach Kahan, Deputy Director Outreach and Member Service; Mackenzie Kuhl, Press Assistant; Una Lee, Chief Health Counsel; Aisling McDonough, Policy Coordinator; Meghan Mullon, Policy Analyst; Juan Negrete, Junior Professional Staff Member; Kaitlyn Peel, Digital Director; Caroline Rinker, Press Assistant; Chloe Rodriguez, Clerk; Kylea Rogers, Staff Assistant; Andrew Souvall, Director of Communications, Outreach, and Member Services; Charlton Wilson, Fellow; Caroline Wood, Staff Assistant; C.J. Young, Deputy Communications Director; Hilary Carruthers, Fellow; Alec Aramanda, Minority Professional Staff Member, Health; Kate Arey, Minority Content Manager and Digital Assistant; Sarah Burke, Minority Deputy Staff Director; Grace Graham, Minority Chief Counsel, Health; Nate Hodson, Minority Staff Director; Peter Kielty, Minority General Counsel; Bijan Koohmaraie, Minority Chief Counsel, O&I Chief Counsel; Clare Paoletta, Minority Policy Analyst, Health; Kristin Seum, Minority Counsel, Health; Kristen Shatynski, Minority Professional Staff Member, Health; and Olivia Shields, Minority Communications Director.

*Ms. Eshoo. The Subcommittee on Health will now come to order.

And due to COVID-19, today's hearing is being held remotely, as well as in person.

In accordance with the updated guidance issued by the attending physician, members, staff, and members of the press present in the hearing room are not required to wear a mask. So we are moving along in the right direction.

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

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

And documents for the record should be sent to Meghan Mullon at the email address we have provided to staff. All documents will be entered into the record at the conclusion of the hearing.

The chair now recognizes herself for five minutes for an opening statement.

Today our subcommittee examines 22 -- everybody hear that right -- 22 mostly bipartisan bills to speed the discovery of more cures, improve patient representation in clinical trials, and enhance the FDA's ability to fulfill its

vital mission of ensuring the safety, efficacy, and quality of America's drug supply. This hearing is an enormous legislative undertaking, and I appreciate the very, very thoughtful work of so many subcommittee members in putting these bills forward.

First we are examining a bill I introduced, H.R. 5585, the Advanced Research Project Agency for Health Act. This legislation would establish ARPA-H as an independent agency within HHS, with a presidentially-appointed director who would have the authority to approve and terminate project funding, establish milestones, and coordinate with other health agencies, including NIH.

ARPA-H will embody the nimble spirit of the highly-regarded and successful Defense Advanced Research Project Agency -- we use the shorthand, DARPA -- to pursue large-scale, high-risk projects. It will break the mold for Federal research agencies by being uniquely focused on solving the valley of death to deliver transformational cures. ARPA-H will correct the gap that currently exists between the basic research pursued by the NIH, and the development of commercial products by the private sector.

With this mission, ARPA-H will drive scientific breakthroughs to improve our nation's health, and help fulfill the President's promise to end cancer as we know it. On Tuesday the President signed into law the bipartisan

Consolidated Appropriations Act of 2022, which provided $1 billion -- that is with a B -- to establish an independent ARPA-H within HHS. This is a momentous first step in creating an agency that will be a beacon of hope for the American people.

But our work isn't done yet. Our committee needs to pass the ARPA-H legislation to provide the agency with the full authorities it needs to be successful from day one, including ensuring that it will be a nimble, dynamic, and independent agency.

Complementing ARPA-H is Representatives Upton and DeGette's Cures 2.0 legislation that they have been working on for three years. It ensures that our Federal public health agencies are working seamlessly together to move new cures through the research stage all the way to FDA approval and Medicare coverage. We have great confidence in what Representatives Upton and DeGette produced in Cures 1.0, so that imprimatur on that legislation and how well it has worked, I think, is foundational in terms of not only their approach, but the confidence that we have in the legislation that they have produced.

Next we are considering three bills to improve the diversity of patients enrolling in clinical trials. All Americans should be confident that their treatments will work for them regardless of race, of gender, or age. But FDA data

shows that, for the drugs approved in 2020, 75 percent of clinical trial participants were White. Only 8 percent of trial participants were African American, 11 percent were Hispanic.

My legislation, the DEPICT Act, would have drug companies demonstrate how they will include diverse populations in their clinical trials by reporting to FDA a diversity action plan with targets by demographic subgroups. It would also give FDA the ability to ask for a post-market study to gather more data if a sponsor does not meet the demographic targets it sets for itself.

Representative Blunt Rochester's ENACT Act and Representative Ruiz's Diverse Trials Act complement the DEPICT Act by addressing the barriers and the burdens that often keep patients from being able to enroll in clinical trials.

Finally, but not least, certainly, Chairman Pallone and Ranking Member McMorris Rodgers have each proposed changes to the FDA's accelerated approval program, while several other members have proposed bills to streamline the development and approval processes for drugs, especially for rare diseases and pediatric cancers.

So colleagues, we have a brilliant panel of industry and physician experts to advise us on these bills, as many of them previously -- during our previous hearing on the FDA

drug user fee agreements. And we all look forward to a highly instructive hearing on these important bills.

[The prepared statement of Ms. Eshoo follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. The chair now recognizes the distinguished ranking member of the Subcommittee on Health for five minutes for his opening statement.

Mr. Guthrie?

*Mr. Guthrie. Thank you, Madam Chair. I really appreciate this hearing. And I didn't realize that right before the hearing starts the Zoom goes live, and so I think last time I was -- I didn't realize that until I read in The Hill in Hits and Misses that what I said was live. And I said last time -- I think I told you I had the most boring opening statement that I have probably ever given ready for the last time around.

[Laughter.]

*Mr. Guthrie. And what I will tell is, listening to me read through a list of bills is probably not exciting. I admit that. I can readily admit that.

But what we are doing is exciting, and it is consequential. It is very interesting, and it is -- what we are -- the title of the thing, "Encourage Innovation,'' and innovation going on in the pharmaceutical space, innovation going in the medical device space. The information that is going on in healthcare in this country is consequential, and exciting to me. So hearing me talk about it may not be, but I want to definitely say that what you guys are doing and what our country is doing is absolutely important and

changing people's lives.

So as we begin this hearing, this is a far more exciting opening statement, because we are here today to discuss proposals designed to increase American biopharmaceutical innovation, a goal I think we confidently all say we share. And over the past decade more novel therapies have been approved in the United States than any other country.

The United States is home to the world's leading biopharmaceutical industry, with the Food and Drug Administration approving 50 new therapies in 2017: 27 of the approved therapies were first-in-class drugs; 26 were to treat rare diseases. Of these 50 newly-approved drugs, 76 percent were approved in the United States before any other country.

One of the most publicly reported approvals was Biogen's Aduhelm, through the accelerated approval pathway. This was the first FDA-approved drug to treat Alzheimer's disease since 2003. It is estimated this historic approval would benefit nearly one million out of six million Americans living with early onset Alzheimer's, which now have some hope of treatment against this vicious disease. Approval of this new Alzheimer's treatment through accelerated approval pathway could lead to other potential benefits, including the development of more effective treatments and encouraging investments in finding a cure for this terrible disease.

Despite its real promise, the Centers for Medicare and Medicaid Services is now attempting to only allow access to the approved drug to a very limited patient population. As CMS moves forward with this plan, access to Aduhelm and future FDA-approved Alzheimer's disease treatments would be restricted for Americans with intellectual disabilities, such as Down's Syndrome, and patients with other neurological conditions. This could have a chilling effect on investment in Alzheimer's research moving forward.

Not only is CMS undermining the accelerated approval pathway, but we also have a bill before us today that calls for further restricting the accelerated approval pathway. Instead of adding more red tape, we should be focused on developing policy solutions that are intended to break down regulatory barriers and promote more collaboration between the regulatory community and the private sector, as I am sure we will as these bills move forward.

And I am thankful that my colleagues have included my legislation and several other bipartisan bills in this hearing. My legislation, H.R. 7008, the Pre-Approval Information Exchange Act, would help address what is known as the valley of death, or the time between when a drug or device is approved by the FDA and when it is covered by a payer.

The bill would specifically allow drug and device

sponsors to share key healthcare economic information, including pre-clinical trial results and other important information, with health insurers and other payers before a drug or device is approved by the FDA. This should help patients gain access to potentially lifesaving treatments such as Aduhelm more quickly by giving the marketplace a chance to price in therapies working towards FDA approval.

In fact, the FDA even acknowledged the potential impact these communications could have by releasing guidance in 2018 allowing these communications to occur. Codifying this guidance will instill further confidence in the marketplace, and provide needed regulatory certainty to the companies and payers already engaged in these information exchanges.

I encourage my colleagues to support H.R. 7008, which has broad industry support.

Additionally, in the case of Aduhelm, we should also be promoting policies that will help ensure patients are receiving timely access to breakthrough therapies without significantly increasing the cost of care for our healthcare system.

For example, Representatives Schrader, Mullin, and I have been working on a bipartisan proposal that would permit state Medicaid programs to enter into value-based purchasing agreements. These payment models would have dual benefits. This could promote greater access to some of the most

expensive treatments on the marketplace for lower-income populations, while also helping shield state budgets against having to pay for a drug if it fails to meet its clinical endpoints. This latter point is especially important when we are talking about accelerated approvals.

I look forward to continuing to work with the bipartisan colleagues in advancing this important measure. I also look forward to finding ways to advance the many proposals we are discussing today.

[The prepared statement of Mr. Guthrie follows:]

**********COMMITTEE INSERT**********

*Mr. Guthrie. And I thank you, and I yield back, Madam Chair.

*Ms. Eshoo. The gentleman -- and that is what he is -- yields back. The chair now is pleased to recognize the chairman of the full Committee of Energy and Commerce, Mr. Pallone, for your five minutes of -- for an opening statement.

*The Chairman. Thank you, Chairwoman Eshoo.

Today we are going to discuss 22 pieces of legislation to boost biomedical research and innovation, diversify clinical trials, and improve program integrity at the FDA. While I don't have time to discuss every bill, I did want to mention a few.

First, we have a bill from Chairwoman Eshoo authorizing the creation of the Advanced Research Projects Agency for Health, or ARPA-H. This proposal has the potential to be transformative, and bring about medical breakthroughs that have the power to change our society for the better, and I was pleased to see that the final omnibus funding bill that Congress passed on a bipartisan basis last week, and President Biden signed into law, included $1 billion for ARPA-H. And now this committee must pass comprehensive legislation to properly establish the agency. I hope my Republican colleagues will work together with us on the authorizing language to make ARPA-H as effective as possible.

Next I wanted to highlight some bipartisan bills introduced by members of our committee, as well as legislation from Representatives -- well, we have one from Chairman Eshoo, we have another from Chairwoman DeGette, as well as legislation from Representatives Ruiz and Blunt Rochester to improve diversity within clinical trials, both among clinical trial participants and investigators.

FDA, researchers, and drug manufacturers all have a role to play in improving clinical trial diversity, and I look forward to hearing from our witnesses about how more diverse clinical trials can not only improve health equity, but also improve scientific discovery and the practice of medicine.

The committee is also continuing its work to improve competition and reduce drug prices. A bill from Representative Kuster would make it easier for generic drug manufacturers to ensure their drugs are biometrically equivalent to their brand counterparts. And it does this by improving FDA's communication about the correct proportion of ingredients during the application process. This bill would simplify the process for generic manufacturers, and reduce needless delays, bringing generic competition to market more quickly.

We will also discuss the Accelerated Approval Integrity Act, which I introduced last week. I want to thank Representative Maloney -- I should say Chairwoman Maloney --

for her joining me on this legislative effort.

FDA's accelerated approval program has led to patients getting faster access to medical breakthrough treatments, including treatments of HIV and several forms of cancer. In order to be approved under the accelerated approval program, an investigational drug must have a positive effect on so-called surrogate endpoint. And these endpoints can include a lab measurement, ultrasound image, or a physical sign that is reasonably likely to predict a clinical benefit, but is not itself a clinical benefit.

So after being approved under this pathway, the sponsor is responsible under FDA regulations for conducting a well-controlled clinical trial to confirm that an actual clinical benefit exists for patients. Unfortunately, however, under the current system, some sponsors have failed to conduct trials in a timely manner. For example, take Aduhelm, the Alzheimer's drug that was approved by FDA last June. Here we are, nine months later, and the sponsor has not screened a single patient for its required confirmatory trial.

Other drugs have stayed on the market for eight or nine years without proving a clinical benefit. And as Dr. Cavazzoni testified last month, the process for removing these drugs from the market is cumbersome, and can take months or even years. And patients, I think, deserve to know that the drugs they are taking are safe and effective.

My bill protects patients by providing FDA with the authority it needs to ensure approved drugs provide a clinical benefit. The bill requires that FDA and the sponsors set out a clinical trial protocol before a drug is approved. It also allows FDA to require that the trials are underway prior to approving the drug. And the bill would also improve transparency and streamline the process for withdrawing approval when clinical trials are not conducted with due diligence, or no clinical benefit is shown. These reforms will strengthen the accelerated approval program and help facilitate additional medical discoveries and product development.

So as we look to strengthen program integrity at FDA and improve research and development, it is critical that we ensure that we are not doing anything that could weaken FDA's gold standard for safety and efficacy. We have to be mindful of FDA's resources, and must always put public health and patients first.

So I commend all the members. I couldn't describe all the bills, but these are all excellent bills that we will be considering, and I commend all the members for introducing the bills before us today, and look forward to the discussion.

[The prepared statement of The Chairman follows:]

**********COMMITTEE INSERT**********

*The Chairman. And I yield back the time that remains, Madam Chair.

*Ms. Eshoo. The gentleman yields back. The Chair is delighted to recognize the gentlewoman, the ranking member of the full committee, Representative Cathy McMorris Rodgers.

*Mrs. Rodgers. Thank you, Madam Chair.

*Ms. Eshoo. Good to see you.

*Mrs. Rodgers. We are considering many important bills that support innovation for patients by improving rare disease research, drug discovery, clinical trial diversity, and our nation's health care supply chains. Thank you, Madam Chair, Chairman Pallone, and my colleagues for all the bipartisan work, as we come together to reauthorize several of FDA's user fees.

FDA's authority to collect user fees expires September 30th. And without user fees, FDA's ability to keep pace with innovation for patients will be severely limited. So continuing this committee's bipartisan tradition for this process is extremely important.

This reauthorization also gives us the opportunity to pursue other bipartisan policies related to the FDA that can improve the review process, and ensure new cures receive consistent, timely, and thoughtful review. I am especially encouraged by proposals to ensure that FDA is fully equipped to review drugs manufactured using emerging technologies,

conduct timely and dependable facility inspections, and support more therapies and cures for rare diseases. These bills build on previous bipartisan efforts to address drug quality and shortage issues, and give patients a voice in drug development.

We will also consider several bills for more diverse populations in clinical trials. During the pandemic, through the use of digital health technologies, drug developers across the country were able to use modernized clinical trial protocols that allowed for greater patient involvement for more diverse populations. We should absolutely be building on this work.

The agenda today also includes my bill for Accelerating Access for Patients Act. Drugs approved through accelerated approval meet FDA's gold standard. There is strong bipartisan support for precision medicine and the need for more innovation and more cures, such as ALS.

Accelerated approval is how precision medicines are approved. If we want to have drugs approved that treat diseases before symptoms appear, it requires accelerated approval. And here is why: traditional approval relies on a drug sponsor showing a clinical benefit, such as a longer lifespan, or reduction of clinical symptoms. Accelerated approval relies on a surrogate endpoint, and that is still reasonably likely to predict clinical benefit. So instead of

a drug trial for cancer therapy having to show you live longer, the trial can show that the drug shrinks the tumor.

Accelerated approval also can't be used for just any treatment. It has to be for a serious disease with an unmet need. If we want to realize the promise of precision medicine, such as relying on genetics and proteins to treat diseases early, accelerated approval must be in FDA's toolkit. I cannot support anything that undermines this important pathway.

This committee has sent a strong signal that we want America to be the world leader in medical innovation. The promise of a better life in lifesaving research is here in the United States of America. We want patients to have options and hope, especially when it comes to serious diseases with unmet needs. Look at the 21st Century Cures Act, Right to Try and, most recently, the Act for ALS Act.

Could there be more transparency around the pathway? Absolutely.

Could the pathway be modernized for diseases that may not have a clear surrogate such as ALS?

That is what I want to focus on today, as I discuss my legislation, the Accelerating Access for Patients Act. Let's consider together how we can expand access to promising innovation with the appropriate guardrails in place.

Before I close, I would also like to specifically

address ARPA-H and H.R. 5585. I was disappointed that the spending bill gave $1 billion to HHS to establish ARPA-H, which I fully anticipate will be transferred to NIH. Just six weeks ago, this committee heard that, in order for ARPA-H to be successful, it needed to be independent from NIH. I have raised questions about duplication, accountability, and strategic priorities for ARPA-H. The Senate just moved a different proposal than the one before Energy and Commerce.

So with no consensus in Congress whether ARPA-H is necessary, or how it should be established, it was funded with $1 billion of unauthorized taxpayer money anyway. That is more than we spend each year on block grants to states for mental health.

My concerns remain about accountability and the lack of a clear mission for ARPA-H.

With that, I would still like to emphasize there is a great number of ideas, important ideas before us with strong bipartisan support. I look forward to today's discussion on moving the FDA user fee reauthorization package through committee.

[The prepared statement of Mrs. Rodgers follows:]

**********COMMITTEE INSERT**********

*Mrs. Rodgers. Thank you. I yield back.

*Ms. Eshoo. The gentlewoman yields back. I would just like to just quickly add something about ARPA-H.

I share the gentlewoman's concerns about duplication, about bureaucracy, and the legislation is so designed so that it is not duplicative. And while we have a difference in terms of the dollar amount, it -- well, I -- what I wanted to say more more than anything else is duplication, and a bureaucracy that can really kill the baby in the crib, so to speak, because it is in a place that doesn't advance what ARPA-H does.

So I look forward to working with you, every member on both sides of the aisle, on this issue. And the clarity in the House, I should add, is that ARPA-H should be under HHS, not in NIH, for all of the reasons that an ARPA-DARPA model won't work there. And that is very clear in the House, in the legislation, in the cosponsorship with the leadership in the House, as well.

So I thank the gentlewoman, and we will always work together.

Now, the chair wants to remind members that, pursuant to committee rules, all members' written fabulous opening statements, members, shall be made part of the record. So I think that pleases everyone, right?

I now would like to introduce our witnesses for the

panel.

Dr. Ruben Mesa is the executive director of Mays Cancer Center at UT Health San Antonio, MD Anderson.

Welcome, and thank you for being here.

Dr. David Gaugh is the senior vice president of sciences and regulatory affairs at the Association for Accessible Medicines, AAM.

Welcome back to the subcommittee. We are more than pleased to see you and have you again.

Dr. Lucy Vereshchagina, welcome to you.

She is the vice president of science and regulatory advocacy at PhRMA.

And again, we welcome you back to the committee.

Dr. Cartier Esham is the chief scientific officer and executive vice president of emerging companies at Biotechnology Innovation Organization. We know the shorthand for that, BIO.

And welcome back to the subcommittee.

Dr. Jeff Allen is the president and CEO at Friends of Cancer Research.

Welcome to you, we certainly appreciate your being here today.

And to Dr. Reshma Ramachandran, she is the chair of Doctors for America, the FDA task force, and a physician fellow with the Yale National Clinical Scholars Program at

the Yale School of Medicine.

Welcome back to the subcommittee.

So thank you to each one of you for joining us today. We look forward to your testimony.

For those -- well, everyone is joining us in person, correct? We don't have anyone virtually. I think you know what green stands for. Yellow -- just going to drive your testimony.

[Laughter.]

*Ms. Eshoo. You all know what red means.

So, Dr. Mesa, we will begin with you, and all of our thanks. You are recognized for five minutes.

STATEMENT OF RUBEN MESA, M.D., EXECUTIVE DIRECTOR, MAYS CANCER CENTER, UT HEALTH SAN ANTONIO MD ANDERSON; DAVID GAUGH, SENIOR VICE PRESIDENT, SCIENCES AND REGULATORY AFFAIRS, ASSOCIATION FOR ACCESSIBLE MEDICINES; 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; JEFF ALLEN, PH.D., PRESIDENT AND CEO, FRIENDS OF CANCER RESEARCH; AND RESHMA RAMACHANDRAN, M.D., CHAIR, DOCTORS FOR AMERICA FDA TASK FORCE, PHYSICIAN-FELLOW, YALE NATIONAL CLINICIAN SCHOLARS PROGRAM, YALE SCHOOL OF MEDICINE

STATEMENT OF RUBEN MESA

*Dr. Mesa. Good morning. Thank you, Chairwoman Eshoo and Ranking Member Guthrie for the honor of participating today. I am Dr. Ruben Mesa. I am a hematologist and oncologist, a researcher, and a member of the national board of directors for the Leukemia and Lymphoma Society.

But more than that, I am a son of a father lost to lung cancer, the son of a breast cancer survivor, and I have dedicated my life's work to changing the devastating effects of cancer. Over that career I have been the principal

investigator or co-investigator on more than 100 clinical trials. Today at the NCI-designated Mays Cancer Center in San Antonio, where I am the executive director, we are providing access to nearly 200 cancer clinical trials to patients in our region in South Texas.

Clinical trials are not a luxury for patients, but are essential for us to be able to provide the very best care for cancer patients. Breaking down barriers to clinical trial participation not only promotes health justice, it is good science. I will give you one example.

The community served by Mays Cancer Center is roughly five million individuals, of which nearly seven percent have Hispanic heritage. So these issues are central to our mission. Breast cancer colleagues have found that a genetic variant near the estrogen receptor 1 gene is associated with breast cancer risk in Latinas of indigenous origin, but is absent in Latinas of mostly European or African genetic ancestry. This genetic variant, which is associated with lower risk of developing breast cancer, could not have been identified in a study without Latina patients. This discovery could lead to new treatments that could both help Latina and non-Latino breast cancer patients.

The lack of diversity across clinical trials today and the systemic under-representation of certain groups weaken our ability to develop new therapies that could improve on

existing treatments. We miss the learnings like we found related to genetic differences in breast cancer. If we want new and better treatments for cancer and other diseases, this is not a problem we can afford to ignore.

Indeed, if we ignore this challenge, we will see trials that take longer and provide less reliable data. We will be less certain if a drug will help cure a certain group, or whether another group will have unexpected or severe side effects. And we will see more trials that fail to enroll enough patients to ever know whether a promising therapy is a breakthrough or not. And that potential breakthrough may very well go back on the lab shelf.

My message for each of you today is we don't have to accept that future. On the agenda today are a handful of bills aimed at tackling these big challenges. The DEPICT Act would require trial sponsors to incorporate diversity action plans early in the trial design process to ensure that trials are built with all patients in mind. Trial sponsors would look at the demographic groups to make up their intended patient population, and then incorporate trial plans to recruit and retain patients from those same groups to ensure that trials don't fail to gather data that would shape how a treatment is used in the real world.

At Mays Cancer Center, in 2013, we mandated a similar process, and we have increased Hispanic patient enrollment in

our interventional studies by more than 20 percent to total almost 60 percent. The DEPICT Act would also hold FDA accountable for modernizing trial rules that too often create additional barriers to trial participation, and it would empower community barriers -- community providers to hire and train trial facilitation staff and implement the IT systems necessary to seamlessly educate and enroll patients.

The Diverse Trials Act would enhance the ability of trial sponsors to work with trial participants to decentralize trial services by leveraging technology to move certain activities into a patient's home. The Diverse Trials Act would clarify that sponsors can offer trial-relegated digital technologies, transportation, lodging, and meals to trial participants without the threat of legal action. At Mays Cancer Center patients come from several hundred miles across south Texas, so these proposed changes could really help our patients from the Rio Grande Valley, the majority of whom are Latino and face many health disparities.

Cures 2.0 would promote public awareness of trials as a treatment option, calling on experts at the GAO and within HHS to recommend actions that would promote diversity in trial enrollment, and make clinical trials more patient friendly.

Of course, there is no silver bullet for fixing the current lack of diversity in clinical trials. This effort

will take sustained attention and willingness to act intentionally, but the results would be life-changing, improved outcome for patients, more and better therapies proven to be safe and effective, more years for patients to be with their families living full and healthy lives. You could take real and meaningful steps today toward that future, and I hope you will.

Thank you again for the opportunity to share my thoughts. I look forward to answering any questions you may have. Thank you.

[The prepared statement of Dr. Mesa follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Dr. Mesa. I can't help but think on this whole issue of diversity in the clinical trials that when I first came to Congress women were not included in trials. Now we find that to be almost laughable at this stage of life in our country. So look at the progress that we have made.

But we have more to do. So -- and we will, with the help of all of the members of this very important subcommittee.

Next, Mr. Gaugh, you have five minutes for your testimony. Welcome again.

STATEMENT OF DAVID GAUGH

*Mr. Gaugh. Chairwoman Eshoo, Ranking Member Guthrie, and members of the subcommittee, thank you for the opportunity to testify about the slate of FDA-related legislation your subcommittee is considering today, and the interplay these bills will have with both GDUFA and BsUFA programs. My name is David Gaugh. I am senior vice president for sciences and regulatory affairs at the Association for Accessible Meds. I am a licensed pharmacist, with many years of experience with both generic and biosimilar drug industries.

AAM and its Biosimilar Councils strongly support timely congressional reauthorization of the user fee agreements. GDUFA and BsUFA aim to put FDA's generic and biosimilar drug program on stable financial footing by enabling FDA to assess user fees to supplement funding appropriated by Congress to fund critical and measurable enhancements which provide greater predictability and efficiency 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. For 10 years now, these user fee programs have played a critical role in increasing patient access to more affordable, generic, and biosimilar

medicines. GDUFA and BsUFA have substantially increased resources available to FDA to review these applications. In turn, FDA and industry have been able to significantly increase access and affordability, with generic and biosimilar medicines providing more than 2 trillion in savings to patients and healthcare systems over the past 10 years.

GDUFA 3 and BsUFA 3 are the culmination of months of negotiation, have been subject to public review and comment, and represent a careful balance between all stakeholders. The commitment letters were carefully negotiated to balance the program enhancements and the resources required to be provided to the FDA. The agreements include a year-over-year Capacity Planning Adjustor, or CPA, that allows FDA to automatically add additional full-time equivalents, or FTE, resources when increased workload criteria from the previous year exceeds expectations.

Therefore, AAM would have concern about adding policies into the reauthorization package that require additional FTEs to implement if the package does not also include corresponding appropriations. Adding such policies would increase industry's year-over-year cost, which was negotiated and agreed upon with the FDA by the CPA.

With that context in mind, AAM and the Biosimilars Council appreciate the opportunity to testify on proposals

relevant to the generic and biosimilar industry, and engage with members on these areas of interest.

In my written testimony I provided specific feedback on proposals noticed in today's hearing that could impact access to high-quality, more affordable generic and biosimilar medicines.

In closing, we strongly support timely reauthorization of GDUFA and BsUFA. We look forward to working with members of both parties to accomplish this goal. We are grateful to the committee's thoughtful oversight of the key issues affecting the user fee programs. And with that I will close and thank you for the opportunity to testify, and I look forward to any questions you might have. Thank you.

[The prepared statement of Mr. Gaugh follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Wonderful, thank you, Mr. Gaugh.

Next, Dr. Vereshchagina, you are recognized for five minutes.

STATEMENT OF LUCY VERESHCHAGINA

*Dr. Vereshchagina. Good morning, Chairwoman Eshoo, Ranking Member Guthrie, and the members of the subcommittee. My name is Lucy Vereshchagina. I am 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 companies, which are devoted to researching and developing medicines that enable patients to live longer, healthier, and more productive lives. I am pleased to appear before you today on behalf of PhRMA, and we welcome the opportunity to discuss the various policy proposals under consideration by the committee.

PhRMA's key priority remains timely reauthorization of the Prescription Drug User Fee Act, PDUFA, and the Biosimilars User Fee Act, BsUFA, prior to the expiration of these programs later this year. These programs are critical for ensuring patients have timely access to lifesaving medicines. PhRMA and its member companies strongly support the PDUFA 7 and BsUFA 3 agreements, as negotiated, and are committed to working closely with Congress, FDA, and all stakeholders to ensure the continued success of these programs.

The agreements were carefully considered by the

biopharmaceutical industry and negotiated with FDA to ensure that the agency is equipped with the necessary resources to help us deliver new treatments and cures to meet patients' unmet medical needs. These agreements were negotiated in a transparent manner with patient organizations, and other engagements with FDA through dedicated stakeholder discussions and public meetings. As such, we would be concerned with any policy proposals and legislative riders that would undermine the negotiated user fee agreements and threaten timely passage.

There are several policy areas under consideration at the hearing today and -- that I would like to highlight.

First, as the committee is considering legislative changes to the accelerated approval pathway, it is important to note that this pathway has provided timely access to more than 200 treatments for HIV AIDS, cancers, and rare diseases. These products are approved under the same rigorous standards of safety and efficacy as traditional approvals.

Moreover, PDUFA 7 requires FDA to update their review process, including earlier discussions in agreement with sponsors on post-marketing requirements for drugs and biologics approved under this pathway.

PhRMA member companies are committed to providing patients with safe, effective, and high-quality, innovative therapies, and accelerated approval pathway helps further

this goal. It is this critical tool for patients and regulators, and the industry continues to support the pathway in its current form.

Second, preserving incentives for rare disease drug development, including those under the Orphan Drug Act, are critical for continued research and development that is providing hope to millions of Americans with rare diseases who still do not have access to FDA-approved treatments. Rare pediatric cancers, in particular, are a very challenging area of research and development, presenting unique scientific, ethical, and logistical considerations.

The last user fee reauthorization in 2017 included new requirements for pediatric studies of certain oncology drugs. It also requires U.S. Government Accountability Office to study and report to Congress on the effectiveness of these new requirements. And as the original provisions went into effect less than two years ago, additional time is needed to fully realize the full impact on pediatric oncology drug development.

It would be premature to make any changes or impose additional requirements while FDA and industry continue to implement these provisions, and before the GAO assessment report is completed in August of 2023.

Third, PhRMA believes that increasing diverse enrollment in clinical trials is a critical step when increasing access

to medicine and improving health outcomes. We believe enhancing clinical trial diversity is a critical component in a broader effort to address deeply-rooted disparities across the U.S. healthcare system. PhRMA and our member companies are enhancing diversity in clinical trials through a number of meaningful steps. Making a real change in clinical trial diversity requires all stakeholders, including industry, patient and community organizations, medical providers, policymakers, and regulators to work together to address the existing challenges.

PhRMA shares the goals of enhancing diversity in clinical trials, and our members are taking action to do so. But policies that would create additional mandates would reinforce, rather than help overcome, known barriers to participation for patients, and have serious unintended consequences, including unfeasibly large and long studies, delayed access to medicines, and disincentives for industry to invest in high-risk therapies areas.

In conclusion, PhRMA urges Congress to reauthorize PDUFA and BsUFA in a timely manner to protect against any disruption to these critical programs. We look forward to continue to work with committee, Members of Congress, and other stakeholders on these important issues.

Thank you for the opportunity to provide this testimony, and I would be happy to address any questions.

[The prepared statement of Dr. Vereshchagina follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you very much, Doctor.

I just thought, Mr. Gaugh, are you -- I hope you are not feeling in any way diminished. You are surrounded by doctors at the witness table.

[Laughter.]

*Ms. Eshoo. So now, let's see, Dr. Esham, you are recognized for five minutes. It is good to see you, and thank you.

STATEMENT OF CARTIER ESHAM

*Dr. Esham. Good morning. Good morning, Chairwoman Eshoo, Ranking Member Guthrie, Chairman Pallone, and Ranking Member McMorris Rodgers, 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 is the world's largest trade association representing biotechnology companies, state biotechnology centers, and related organizations across the United States and in more than 30 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.

We appreciate the opportunity to speak with you today about key priorities we believe will enable biopharmaceutical companies to modernize the clinical development paradigm to one that is more patient-centric, effective, and inclusive, and needed to develop next generation medicines that will improve the lives of the patients and their families that we serve.

We also want to take this opportunity to urge timely reauthorization of PDUFA 7 and BsUFA 3 that will serve to advance those goals, as well as improve regulatory transparency, oversight, and ensure that the FDA is best able

to carry out its vital mission to protect and promote public health.

Congress has built a strong foundation over many years that have collectively worked to ensure effective and timely reviews, improved drug and biologic safety monitoring, enable the agency to keep pace with medical and scientific advancements, and provided the support necessary to ensure that advanced medicines are provided to patients as quickly and safely as possible. We look forward to working with this committee to build on those efforts as we discuss the user fee agreements and proposed legislation under consideration.

The PDUFA and BsUFA agreements will build upon these previous efforts and foster next generation scientific efforts. For example, PDUFA 7 will continue to advance the utilization of patient-centric drug development and review processes, expand our ability to utilize real-world evidence, strengthen the FDA safety monitoring capabilities, and ensure that the FDA is able to meet the demands and opportunities of the digital age by improving the agency's analytical capabilities, and supporting the use of digital technologies, which have the potential to reduce patient burden and more effectively capture information about clinical outcomes for all patients.

I would also like to take this opportunity to convey BIO's commitment to improving clinical trial diversity. The

COVID pandemic highlighted the urgent need to remove barriers and advance solutions that enable clinical trials to be more representative of the patients being treated. It also highlighted methodologies, tools, and approaches that have the potential to tear down some of those barriers. PDUFA 7 will advance the acceptance of real-world evidence and data and digital technology tools, which we believe are key to advancing a clinical development ecosystem that is more expansive, inclusive, and less burdensome to patients.

We have also provided this committee with legislative proposals we believe would further remove barriers and establish a regulatory framework that will drive change and support a clinical development ecosystem that is more inclusive and representative of the patients we serve, including establishing processes and understandings about how and when to establish enrollment targets, new approaches to inclusion and exclusion criteria, how to design and implement trials that are less burdensome to patients, and better enable evidence collection that improves our collective understandings of health outcomes for all patients.

Before I close, I would also like to convey our continued support for the accelerated approval pathway. As previously mentioned, well over 200 drugs and biologics to treat serious or life-threatening diseases or -- and conditions with high unmet medical needs have been approved

using this pathway, extending lives in certain cases and saving lives by providing novel therapies that met FDA's well-established approval standards for safety and effectiveness earlier than would have been possible without its existence.

The PDUFA 7 agreement includes commitments that will further strengthen this pathway by advancing regulatory understandings about what is necessary to support the utilization of a surrogate endpoint as a basis for approval. It includes revisions to improve processes to allow for more effective dialogue and design of assessments of PMR needs and study designs, and improve the continued evaluation of PMR post-approvals to ensure requirements are being met and/or remain scientifically valid.

We look forward to working with Congress to ensure timely enactment of PDUFA 7 and BsUFA 3, and are committed to working to advance a new clinical development paradigm that is more expansive, inclusive, patient-centric, and supports the development and timely delivery of next generation medicines that will improve the lives of patients and their families. Thank you.

[The prepared statement of Dr. Esham follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Dr. Esham.

Dr. Allen, you are recognized for your five minutes of testimony, and welcome again, and thank you.

STATEMENT OF JEFF ALLEN

*Dr. Allen. Thank you, and good morning, Chairwoman Eshoo, Ranking Member Guthrie, and members of the committee.

*Ms. Eshoo. Move your microphone a little closer.

*Dr. Allen. Sure.

*Ms. Eshoo. We don't want to miss a word.

*Dr. Allen. All right, thank you. I am Jeff Allen, president and CEO of Friends of Cancer Research, an advocacy organization dedicated to the acceleration of science and technology, from bench to bedside. Thank you for holding this important hearing to modernize numerous aspects of regulation and research.

This is a unique opportunity to address a diverse set of issues critical to making progress against illnesses like cancer, neurological disorders, and the over 6,500 rare diseases that currently have no treatments.

In order to improve the government's capability to speed research, this committee has taken on the important work to authorize the Advanced Research Project Agency for Health. We believe that ARPA-H can serve a unique role of catalyzing transformational technologies that have broad applicability across multiple disease areas.

An additional effort of this committee is to enhance scientific infrastructure and accessibility to new medicines

through the 21st Century Cures Initiative. The Cures 2.0 bill, championed by Representatives DeGette and Upton, builds on numerous provisions of its predecessor that have proven to be highly effective at promoting development and facilitating access to innovative therapies. While efficient processes and a robust research infrastructure are necessary, barriers to clinical trials present a perennial challenge.

For decades, the average enrollment of adults with cancer in clinical trials has hovered around two to eight percent. Several of the bills included in today's hearing will help make clinical trials more inclusive, accessible, and equitable. Many of these would grant more people access to trials as part of their care, and provide clinical evidence for a more representative population.

While there are many topics being discussed today, several of which I have addressed in my written testimony, I want to focus today on efforts to optimize the accelerated approval process. Accelerated approval allows for a drug to come to market based on a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit and, it is reserved for drugs to treat serious and life-threatening conditions. This broadly applies to all drug classes.

However, due to available surrogate endpoints and the scientific advancements to treat cancer in the past 10 years, 80 percent of the accelerated approvals were granted for

oncology indications. A recent assessment by the FDA concluded that cancer therapy is receiving accelerated approval, where available, a median of 3.4 years earlier than if approval were based on a full clinical endpoint, such as overall survival.

Products approved through the accelerated approval process are subject to post-approval study requirements to verify the anticipated effect of the drug. In evaluating the total number of indications that have received accelerated approval, 49.3 of all indications have been converted to full approval based on subsequent evidence. Conversely, only 9.9 percent of accelerated approvals have been withdrawn. This yields 40.8 percent of pending indications that have neither been converted nor withdrawn. Together, this indicates a highly favorable success rate for confirmation of benefit, and demonstrates the importance of timely post-approval studies.

In evaluating the time needed to develop post-approval evidence, studies resulting in conversion to full approval took a median of 3.1 years. Withdrawals occurred at a median of 3.8 years. Of the pending oncology indications, 72 percent have been approved in the last 2 years. Given that it may take three to four years to develop the necessary data, it may be unrealistic to expect these pending studies to have already been completed.

These data indicate that the accelerated approval is working as intended. It has enabled patients with serious diseases to have access to new medicines years earlier. But this pathway can and should be improved to maximize the benefits. Key to continued success is both early planning when accelerated approval may be used, and transparency to robust, post-approval evidence generation. Together, this will enhance confidence in the process and bolster the ability to address unmet needs for patients.

Through the leadership of this committee, we can enable a strong research and evidence infrastructure, implement clinical trials that are more equitable and accessible, and ensure that avenues are available to speed access to promising new, safe, and effective medicines. For the millions of patients across this country who are currently dependent on safe and effective medicines, and for those who are holding strong for the breakthroughs to come, there isn't time to waste.

Thank you, and I look forward to answering your questions today.

[The prepared statement of Dr. Allen follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you, Dr. Allen.

And last, but not least, Dr. Ramachandran, for your five minutes of testimony. And again, thank you, and welcome back.

STATEMENT OF RESHMA RAMACHANDRAN

*Dr. Ramachandran. Thank you. 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 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 towards ensuring meaningful clinical outcomes for our patients. My remarks reflect my own views, and not that of my employers nor the organizations I work with.

While I understand that the subcommittee is considering several bills related to enabling access to innovative, safe, and effective health technologies, my remarks today will be focused on just two areas.

First, reforms to the accelerated approval pathway that rebalance early access to promising treatments with oversight to ensure that these treatments are truly effective and safe are urgently needed. Nearly half of the 253 accelerated approval drugs approved by the FDA between 1992 and 2020 have not been confirmed to be clinically effective. Just last year, the FDA maintained marketing authorization of four cancer drug indications, despite their required post-approval

studies failing to confirm clinical benefit.

Moreover, relying on real-world evidence to confirm clinical benefit has not been shown to work. Of the 50 required confirmatory trials for drugs granted accelerated approval by the FDA between 2009 and 2018, none could be feasibly emulated using available real-world evidence.

Such a lack of oversight by the FDA in allowing manufacturers to continue to market unproven drugs can lead to harms for our patients and us, as clinicians.

First, we may be unknowingly prescribing treatments of limited or no meaningful benefit to our patients. For those conditions where there may be an available and proven alternative, this may create an unfortunate opportunity cost for patients, both therapeutically and financially.

Second, payers may be required to provide coverage for such treatments, causing patients prescribed these drugs to incur costly out-of-pocket payments, and other beneficiaries to potentially pay higher premiums.

Reforms within the Accelerated Approval Integrity Act offer a crucial opportunity to recenter the expedited review pathway around patients. Importantly, the bill would enable FDA oversight over the design and start of post-approval studies to prevent against any delays in initiating confirmatory trials, and ensure that these required studies examine the critical question of whether these drugs are

truly beneficial for our patients.

Sponsors would also have to routinely report to the FDA on progress in completing these studies, allowing the agency to assist if there are any roadblocks. Should the drug fail to show clinical benefit, or their sponsors lag behind in completing required post-approval studies, FDA would be able to withdraw these accelerated approval drugs more efficiently and prevent patient harm.

Finally, accelerated approvals where sponsors either fail to confirm clinical benefit or fail to report their progress in doing so will automatically be withdrawn after an ample period of time.

This robust legislation could be strengthened even further. Namely, FDA, in having oversight of post-approval study design, could also ensure that clinical endpoints are being studied, not surrogate ones, and definitely not the same ones that are used in trials supporting accelerated approval.

Reports submitted to the FDA on progress in completing post-approval studies should also be made public, and any results from these studies should be made immediately available. Not only would this enable public accountability of such approvals, but it would also inform how we, as clinicians, take care of our patients, especially if a drug is found not to be beneficial.

Further fueling uncertainty of whether FDA-approved treatment is beneficial for patients is a lack of representation within clinical trials. To date, FDA's laudable efforts to address these gender, age, and racial disparities in clinical trial enrollment have fallen short in moving industry sponsors to act. Data from the FDA's drug trial snapshot, a publicly-available webpage with demographic information of participants enrolled in pivotal trials of newly approved drugs and biologics, showed only 20 percent reported clinical benefits and risks for Black patients, a figure that did not improve over the eight-year period that was assessed.

The DEPICT Act includes provisions to ensure that industry sponsors not only promise to enroll diverse and representative participants into clinical trials, but actually do so, by setting clear targets for enrollment based on disease prevalence data. Should sponsors fail to enroll trial participants representative of the patients who would be ultimately prescribed the treatment, FDA would then require post-approval studies to demonstrate treatment benefit across various demographic subgroups. Should disease prevalence data not be available, FDA should set a floor for clinical trial enrollment targets that reflect available national demographic sub-population data.

In my written testimony I further discussed these areas

and others being considered by the subcommittee where legislative action could have a profound impact on improving the lives of my patients and the American public.

Thank you again for this opportunity. I am happy to answer any questions you might have.

[The prepared statement of Dr. Ramachandran follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. Thank you very much, Doctor. Now, so this -- colleagues, this concludes the testimony of our witnesses. We will now move to member questions. And I recognize myself -- surprise, surprise -- for five minutes. How is that?

And I am going to start with one of my favorite subjects to set the stage. Let me ask each witness, do you support H.R. 5585? That is the ARPA-H legislation.

Dr. Mesa?

*Dr. Mesa. Yes, I do.

*Ms. Eshoo. Mr. Gaugh?

*Mr. Gaugh. Yes.

*Ms. Eshoo. Thank you.

Dr. -- I am going to get your name right -- Vereshchagina.

*Dr. Vereshchagina. PhRMA believes that ARPA-H should be narrowly focused on increasing R&D investments in areas of high scientific and regulatory uncertainty that may not be currently pursued by other public or private sector entities.

You talked this morning about avoiding duplication. So that is our comment.

*Ms. Eshoo. Wonderful. I take that as a yes.

Dr. Esham?

*Dr. Esham. Yes, we are supportive of ARPA-H, and with the -- we thank Congress for the enactment and funding the establishment of ARPA-H and the funding for ARPA-H, and we

want to work with you on the bill, now that that law has been passed, to sort of, you know, ensure that -- as you said, we do think it is very important that this agency has the ability to act independently, and has the -- and able to embark on the nimble spirit, I believe was your turn of phrase, which I think we very much relate to, to ensure it is able to best meet its unique and transformative mission.

*Ms. Eshoo. Wonderful. Thank you, Doctor.

Dr. Allen?

*Dr. Allen. Yes. We support the formation and authorization of ARPA-H.

*Ms. Eshoo. Wonderful.

And Dr. Ramachandran?

*Dr. Ramachandran. You can call me Dr. Ram.

[Laughter.]

*Dr. Ramachandran. Yes, I support the ARPA-H, especially if it includes provisions to ensure that access and affordability are built into the innovation model, so that Americans and taxpayers can benefit from federally-funded research.

*Ms. Eshoo. Thank you very much.

Now to Dr. Mesa, as you said in your testimony, you are a principal investigator of more than 100 clinical trials. So you have incredible experience in this area. Do you support 6584, the DEPICT Act? Do you think that this is

directed and shaped to produce the outcomes that we are looking for, given your vast experience?

*Dr. Mesa. Yes, I think it could be a very impactful bill. As we think about the barriers that patients can face for diversity in clinical trials, I think there is many aspects of it that can be very impactful.

First, recognizing that there is not one solution.

*Ms. Eshoo. Right.

*Dr. Mesa. You know, as we look at patients, they are all different. They all have different complexities. They all have different barriers, you know. So trying to create parts that really focus on the patient's part of that equation, trying to overcome a lack of health literacy, pre-conceived notions about clinical trials, trying to overcome personal aspects in terms of barriers to care, transportation limitations --

*Ms. Eshoo. Yes.

*Dr. Mesa. -- you know, telemedicine solutions for increasing feasibility, so there is really a patient piece to this.

The second part is really in the conduct of the trial itself, how the trial is designed, its eligibility criteria. I will use, for example, there are certain boilerplate eligibility criteria that sometimes can really be pre-discriminatory, such as relates to hepatic function or liver

function. There is higher rates of elevated liver function tests in South Texas that can just kind of automatically start to exclude a group of patients.

*Ms. Eshoo. Let me -- because I only have 5 minutes, and I have 1:12 left, does the FDA currently have any legally-binding standards for diversity in clinical trials?

*Dr. Mesa. Unfortunately, there is no minimum standard at the current time.

*Ms. Eshoo. Now, at the Mays Cancer Center you require that each new trial put in place -- the abbreviation is M-A-P, MAP, Minority Accrual Plan. That includes enrollment projections, demographics, specific strategies. This is, I think, very similar to the Diversity Action Plan.

Can you tell us how what you are doing with MAP, M-A-P, how that has led to new scientific discoveries if, in fact, that has happened, and -- or how it has affected enrollment in the trials?

*Dr. Mesa. So I will use an example for a disease that is over-represented in African Americans, multiple myeloma --

*Ms. Eshoo. Right.

*Dr. Mesa. -- where the Minority Action Plan for those trials specifically included outreach to African American churches, you know, and other groups in our community in south Texas to increase awareness and try to decrease barriers.

*Ms. Eshoo. Excellent. Well, my time has expired, so thank you to each one of you.

The chair now recognizes our wonderful ranking member, Mr. Guthrie, for his five minutes of questions.

*Mr. Guthrie. Thank you, Madam Chair.

First, I have a letter in support of my bill, 7008 H.R. (sic) that has been given to the staff, your --

*Ms. Eshoo. So ordered.

[The information follows:]

**********COMMITTEE INSERT**********

*Mr. Guthrie. Okay, thank you. And I would like to especially thank the Academy of Managed Care Pharmacy for their support on the letter.

So, Dr. Vereshchagina, I want to ask you these questions. So the intent of the pre-approval information exchange is not so PhRMA can advertise before a drug is out. That is absolutely not the intent -- before it is approved. But for healthcare plans -- so plans, payers -- to have the information, knowing what is coming down the pike, so we can get payment. So getting approval of a drug without payment of a drug sometimes keeps people from having access to a drug. And so what we want to do is shorten that time, the valley of death, particularly blockbuster drugs moving forward.

And I know that has been shared -- interest shared by the FDA. So in 2018 they put guidance. And so my question, Dr. Vereshchagina, is there -- what has been the experience of your member companies since the guidance has come out in 2018?

*Dr. Vereshchagina. Thank you for the question. So, as you mentioned, the FDA finalized the guidance on the issue, and our member companies find this FDA guidance very helpful and very impactful. And in fact, between 2017 and 2021 the number of publicly-announced, value-based contracts has more than doubled. So we are seeing real positive impact of FDA

giving very clear guidance on this issue.

So in my understanding -- and I am not a healthcare coverage expert, I am an FDA regulatory expert -- but my understanding that many of these contracts showing benefit and reducing patient costs and reducing overall medical costs. And if you would like any additional details or numbers on this, I would be happy to get back to you.

But again, the bottom line, that FDA's final guidance yielded real benefits, and helped manufacturers and payers work together and share the information to make sure that new medicines are accessible and affordable for patients.

*Mr. Guthrie. Well, thank you. As we are -- as I talked about in my exciting opening statement, there -- the innovation that is coming -- and a lot of it is extremely expensive. I mean, it is expensive research. It is expensive to do. Like, you know, the cure that they have now of sickle cell anemia is a bone marrow transplant, I believe. So -- which is fantastic that we can cure sickle cell anemia for people that are suffering from it, absolutely. But having access to it is also important.

And so we are looking at value-based agreements, Dr. Schrader and I, a colleague -- I guess he is on the committee, but he will be here in a little while. We are -- how do you pay for that?

And so I know a lot of the innovators, the

manufacturers, are willing to take on some of the risks to say, hey, this cannot meet the clinical desire that we have. So like a Medicaid system, instead of paying everything up front, may pay over time. And if they don't get the results, then have to pay -- then they don't -- it is pay-for-performance sort of, I guess, value, the value of it.

And so how would -- the problem is that is not just you setting a price, and then the payer deciding whether or not they want to meet the price, and negotiating over a price. It is negotiating over a lot of issues to come up with the value-based agreements. So how would information pre-approval be beneficial to value-based agreements?

*Dr. Vereshchagina. So as I mentioned, I am not a expert in value-based contracts or coverage overall, but transparency and open communications and ability of industry, working with FDA and sharing the information, has been helpful and, as I mentioned, from the numbers we have seen, really resulted in a tangible improvement in the sharing of the information.

*Mr. Guthrie. Okay, thanks. So the idea is that, if a drug is going to be approved, we see it is on the pathway to being approved -- well, the issue is, once a drug is approved, you don't really get -- a lot of people don't get access to it until it is paid for. Do they have access to it -- somebody to help their insurance to pay for it, or the

payer pay for it? Because it is just -- a lot of it is just too expensive.

And so, if you can see a drug move into approval, and you can have those discussions over -- beforehand, it shrinks the valley of death, as it is called, or the difference between the day the drug is approved and the day the payer has it in their formulary to pay for. And that is the intent, and that is what we are trying to do, not trying to push FDA to approve drugs that aren't ready to be approved, but having the gap between access to a blockbuster drug and -- approval of blockbuster drug and access.

So thank you very much, and I will yield. And I will yield back.

*Ms. Eshoo. The gentleman yields back. The chair now recognizes the chairman of the full committee, Mr. Pallone, for your five minutes of questions.

*The Chairman. Thank you, Chairwoman Eshoo. At our hearing last month, Dr. Cavazzoni from FDA explained how it would be helpful to allow FDA to require drug sponsors of accelerated approval drugs to begin their confirmatory trials before the drug is approved, and the current cumbersome process that FDA has to follow to withdraw an approval from a drug that has not shown a clinical benefit for patients. And with that in mind I introduced H.R. 6963, the Accelerated Approval Integrity Act, that I mentioned in my opening

statement.

So I wanted to ask Dr. Ramachandran, can you describe why it is important for patients and providers that manufacturers complete these confirmatory trials in a timely manner?

And what policies would ensure that drugs that do not complete their confirmatory trials come off the market?

*Dr. Ramachandran. Yes. Thank you so much, Chairman, for the question.

It is critically important for our patients and us, as clinicians, to know the true benefit and safety, especially for these drugs that are being approved fairly early on, and are allowing us earlier access to them.

The reason why these post-approval studies were so important is that we are prescribing these drugs with a lot of uncertainty to our patients. And so having these studies completed in a timely manner, and knowing exactly that they are truly clinically beneficial, that that surrogate endpoint that the drug was initially approved on is predictive, and does demonstrate clinical benefit for our patients is important.

If it doesn't show that, and it continues to linger on the market, unfortunately, you know, if there is a proven alternative option, our patients won't be accessing that. Instead, they might be stuck on this accelerated approval

drug with no clinical benefit or, worse, something that might be potentially unsafe. On top of that, the financial ramifications are pretty incredible for patients who are taking drugs of unproven benefit.

As an example, there is a drug called pembrolizumab, which is a cancer drug for liver cancer and also metastatic urothelial cancer, where the post-approval studies were actually found to be negative. FDA continued to let the drug on the market, and it cost patients about $13,000. This is before insurance, of course, but high, very high co-pays per month to be able to access this drug. So the financial ramifications for both patients and payers are pretty incredible.

Some of the provisions that were in the bill that you have introduced are very strong, in terms of allowing and making sure that there is FDA oversight in terms of the study design, but more importantly, ensuring that there is a process, and with clear criteria, for FDA to withdraw these drugs in a efficient manner, so that patients aren't incurring these harms.

And the automatic expiration provision is particularly critical to make sure that these drugs aren't lingering while we are waiting for sponsors and the FDA to kind of go back and forth in terms of whether or not the drug should continue to stay on the market.

*The Chairman. All right, let me ask you another question. There are proposals before us today -- you know, bills today -- that address the accelerated approval pathway in a different way. And I am concerned that these measures may unintentionally lower current standards for safety and efficacy.

So can you describe the importance of having a strong safety standard and a clear efficacy standard for the accelerated approval pathway, and the risk to patients if we go too far in opening up this accelerated approval process?

*Dr. Ramachandran. Yes, there has been some proposals to allow for real-world evidence or observational data, both in Cures 2.0 and in other legislation that would be enough to fulfill the post-approval studies that are required for accelerated approval. Unfortunately, we have done a number of studies -- or our research group at Yale -- that have shown that, if we try to replicate those confirmatory trials using real-world evidence or observational studies, we are not able to do so.

So, you know, with the currently-available real-world evidence, it is not sufficient to be able to show clinical benefit or safety. And having, you know, robust study design is incredibly important for us, as clinicians, to know that it is actually preventing death or hospitalization, things that matter for our patients, instead of taking something

that could be potentially toxic or unsafe, and not just -- might not work.

And, you know, I should remind folks that, you know, chemotherapy, you know, that is often times used for cancer treatment, it is not an easy drug to take. Our patients suffer incredible side effects from taking these types of medications, even though they might be lifesaving. So the longer period of time we allow for patients taking these drugs that might be unproven, but on top of that have very, very, you know, serious side effects on the market, it takes a toll on them. And you can imagine what sort of false hope it could bring if the drug is found to be unproven, but still allowed to be on the market by the FDA.

*The Chairman. Now, I think you mentioned the use of real-world evidence, so just -- there is only 30 seconds, but --

*Dr. Ramachandran. Yes.

*The Chairman. -- what does the current data say about researchers' ability to prove the clinical benefit of accelerated approval based on real-world evidence?

*Dr. Ramachandran. It is very limited, at least with current sources that we have. We did a study actually looking at real-world evidence for a number of drugs, accelerated approval or otherwise. And we only found that 15 percent of the trials could be replicated with real-world

evidence, suggesting that that data source is just not sufficient right now, in terms of being able to show true clinical benefit and safety for patients.

*The Chairman. All right, thank you. I yield back. Thank you, Madam Chair.

*Dr. Ramachandran. Thank you.

*Ms. Eshoo. The chairman yields back.

The chair now recognizes the ranking member of the full committee, Mrs. McMorris Rodgers, for your five minutes of questions.

*Mrs. Rodgers. Thank you, Madam Chair.

Mr. Allen, is the accelerated pathway working for cancer therapies and patients who need those treatments?

*Dr. Allen. It is. You know, over the last 30 years, since the pathway was implemented, at least in recent years, an average of 30 percent of all oncology drugs have gone through the accelerated approval pathway. And of those, under 10 percent have failed to confirm their benefit.

I think that this is due -- in large part, due to the efforts of the cancer community to standardize these measures, and research them in order to improve their reliability. What this has resulted in is access to these products years earlier, often times where there was no current available therapy.

*Mrs. Rodgers. Thank you. Some of the witnesses have

suggested that post-approval studies should use clinical endpoints, rather than surrogates. What would this mean for cancer patients?

*Dr. Allen. I think it is a very good point, but it is also worth diving into the data here. In oncology, there have been a couple of instances where a surrogate endpoint, such as tumor size reduction, for example, is used in a number of cases for the basis of an accelerated approval. So that is the surrogate endpoint.

It also has been used in a couple of blood cancers because of the overall impact on those endpoints. Specifically, overall major psychologic response or complete response, meaning the cancer has been eradicated.

So while that isn't the same as a long-term overall survival endpoint, the eradication of cancer, I think, is a notable clinical benefit here. And so I think that is -- these drugs have changed the treatment of certain leukemia. So I don't think this is the area where we need to be focusing the attention of improvements to this pathway.

*Mrs. Rodgers. Thank you.

Dr. Esham, your testimony today speaks to how effective the accelerated approval pathway has been in reviewing and delivering safe and timely therapies to patients with serious or life-threatening conditions. Why has the accelerated approval pathway been so successful for bringing new

therapies to certain patient groups like those with cancer, but not for others, like those suffering from ALS?

*Dr. Esham. Thank you for that question. We have long advocated for the development of surrogate and intermediary clinical endpoints across more disease areas.

We have also advocated for more consistent practices across FDA about what evidence is needed to support the utilization of surrogate and intermediate -- intermediary endpoints in more disease states.

We hope that the provisions in PDUFA 7 that allow for early engagement to discuss issues and criteria to support the utilization of surrogate endpoints to support approval will help.

We also hope that the pilot program on rare disease endpoints will advance mutual understandings about how to meet these criteria and enable utilization.

It is also important that the medical, patient, scientific, and regulatory community work together to ensure that scientifically sound surrogate endpoints are developed, and that specific guidance is provided about how to utilize those types of endpoints in more disease states such as ALS.

Each approval and accelerated approval does allow for more timely access to treatment. It enables scientific understandings of diseases to advance, and can be foundational to continued innovation and investment in

serious, complex, and life-threatening diseases such as ALS.

*Mrs. Rodgers. In the last 15 years, 56 percent of companies that received an accelerated approval were small companies. What factors go into whether a small company decides to pursue the accelerated pathway for a novel drug?

And how could the threat of civil monetary penalties or an automatic expiration of approval shape that decision?

*Dr. Esham. The reason I think that you see a large number of emerging companies utilizing the accelerated approval pathways is because they are working on novel areas of treatment, many times an area where there is little precedent established. So the accelerated pathway, again, is the path forward to ensuring that we get these first-time treatments and novel ways to treat patients. And without the accelerated approval, this would be greatly limited.

We do have some concerns and want to work with the committee relating to the establishment of mandatory withdrawal and evaluation timelines, and the potential impact that could have on investment in these types of serious and life-threatening diseases. And while a majority of the treatments, as mentioned in others' testimony today, approved to date under accelerated approval has transitioned to traditional approval under five years, most of those approvals are evaluated based on oncology treatment data. And we have concerns that science hasn't moved the same way

or at the same pace across all disease states.

And even with the potential for waivers, we have uncertainties about whether there would be consistent and understood processes for these evaluations, whether they would be able to be done in a timely manner, and whether they would take into account cases where medicines are continuing to meet benefit risk standards, but more studies are warranted, or will be able to continue to be provided to patients.

But we do want to work with this committee to improve processes and approaches that will strengthen the pathway, and we commit -- our commitment was clear.

And some of the provisions that were included in PDUFA -- again, discussing the criteria for surrogate endpoints, ensuring that there is earlier engagement in the process to determine PMR assessment needs and study designs, and improve processes post-approval to better enable sponsors in the FDA to engage on issue resolution where there are problems with conducting the trial, and to determine if it is still scientifically valid or not -- and that will support efforts around --

*Mrs. Rodgers. Thank you.

*Dr. Esham. -- withdrawal discussions.

And we also are supportive of the utilization of real-world evidence. And while some have said it may not be

the panacea, we are ever moving towards better data sources, and PDUFA does have provisions to continue to advance how we can use real-world evidence to support post-market requirements, which may alleviate some of the barriers that we have seen to date.

*Mrs. Rodgers. Thank you. I really appreciate the opportunity to talk about the importance and the potential of real-world evidence in drug development, especially for certain populations, like those with intellectual disabilities or the rare diseases.

And thank you for the time, Madam Chair. I yield back.

*Ms. Eshoo. You are a beautiful voice for those that you just spoke to, and we all appreciate it.

Okay, we now are going to recognize the gentleman from North Carolina, Mr. Butterfield, for your five minutes of questions.

*Mr. Butterfield. Let me say good morning to all of you, and thank you to the chair and ranking member for including two of my bills in today's hearings. They are H.R. 6972 -- we call it the Give Kids a Chance Act, which was introduced by myself and my fellow co-chair of the Childhood Cancer Caucus, Mr. McCaul. And the second piece of legislation is H.R. 1730, the Speeding Therapy Access Today Act -- we call it the STAT Act -- introduced by my fellow co-chair of the Rare Disease Caucus, my friend from Florida,

Mr. Bilirakis. Both bills, Madam Chair, address critical medical needs, more treatments, and cures for pediatric cancers and rare diseases.

And so I want to continue with you, Dr. Esham, if I can. The Give Kids a Chance builds on the Race for Children Act, which was supported by many, many members of this committee. The bill provides the FDA with the authority to direct pediatric studies of combinations of cancer drugs. And this is important because cancer researchers tell us that it is unlikely that one drug will work for all cancer patients. Many patients, both adults and children, may need combinations, combinations of therapies to fight their disease.

And so, Dr. Esham, thank you for your testimony. Thank you for sharing your industry's commitment to pediatric patients. We are -- well, what are some of the challenges that biotech companies face when making cancer drugs for children?

*Dr. Esham. Thank you for that question. You know, the development of therapeutics for childhood cancer does have its challenges.

Firstly, it is very rare, and the etiology and biology of cancers that occur in children can differ from those that occur in adults. So immediate extrapolation of efficacy and safety is not always possible.

We need to balance the desire to enroll children in clinical trials in recognizing that -- particularly when current modality treatments provide clear benefits. So we don't want children placed at a disadvantage of being enrolled in a clinical trial that has undue exposure to risks, or does not provide the necessary health care.

I will note that, since enactment of the RACE Act, section 504, we have been working diligently with the FDA to remove challenges and try to ensure successful and effective implementation of that program. We are working to establish metrics to make sure that we are taking the opportunity to evaluate successes or challenges. The program went into effect in August of 2020, and implementation guidance was published in 2021. So we are, again, working very diligently to try to ensure --

*Mr. Butterfield. Thank you for that. I am going to have to move onto the STAT Act.

*Dr. Esham. -- effective, yes.

*Mr. Butterfield. I am going to have to move on to the STAT Act in just a moment.

*Dr. Esham. Yes.

*Mr. Butterfield. But let me just say for the record that it is important to just know that the Give Kids a Chance Act -- that the FDA would not be given unlimited authority. I want all of my colleagues to know that, it is not a grant

of unlimited authority. The bill will set rigorous scientific standards and extend waivers and defer protections to those new studies. And so I just want the record to reflect that.

Let's move on to the STAT Act. There are over 7,000 known rare diseases, and yet 95 percent of them do not have an FDA-approved treatment. The STAT Act's goal is to increase rare disease therapy development, and increase access to treatments and cures for patients. One of the pillars of the bill is the creation of a rare disease and condition drug advisory committee, which advocates believe would help strengthen FDA's rare disease activities.

And so back to you again, Dr. Esham, and we have about a minute left. Could you speak to the potential value that engagement with patients and providers and other experts could bring FDA as it reviews rare disease drug applications?

*Dr. Esham. Thank you. And I will say we are still reviewing this legislation, but are committed to working with your office to provide our thoughts. And we are supportive of efforts to ensure that there are clear paths forward for the development of treatments of rare diseases and how to effectively address our unique challenges.

So we look forward to continuing to work with you on --

*Mr. Butterfield. Thank you.

*Dr. Esham. -- on this legislation.

*Mr. Butterfield. Thank you for your cooperation. Thank you for your comments.

And I would like to thank the chair and the ranking member for including in today's hearings bills related to clinical trial diversity. I will soon be introducing legislation with other colleagues Robin Kelly, Tony Cardenas, and Yvette Clarke of New York on clinical trial diversity with NIH-supported trials. I look forward to working with all of you, and I wish all of you a happy St Patrick's Day. I yield back.

*Ms. Eshoo. The gentleman yields back. I can't help but think of this on a consistent basis, Mr. Butterfield. We are really going to miss you, a wonderful member of this committee. But you are not gone yet. You still have --

*Mr. Butterfield. Don't make me sad.

*Ms. Eshoo. -- a lot --

*Mr. Butterfield. Don't make me sad, Madam Chair.

*Ms. Eshoo. I am not going to make you sad.

*Mr. Butterfield. Thank you, thank you.

*Ms. Eshoo. We want to make you glad, by getting your legislation through. So thank you for your --

*Mr. Butterfield. Thank you.

*Ms. Eshoo. -- terrific work. Now the chair is so pleased to recognize the gentleman from Michigan, Mr. Upton.

First, how are you feeling?

*Mr. Upton. Well, I am doing much better today. I -- for those that didn't know, I tested COVID before that Library of Congress event on Tuesday. So I am self-quarantined until Saturday. I want you to know I am studying the books hard, so I hope to pass the test Saturday so I can go back to Michigan.

[Laughter.]

*Mr. Upton. I joined Buddy Carter. I know he tested positive, as well, for that event, so I wish everybody well, for sure.

But thanks for your --

*Ms. Eshoo. Well, please take good care. Please take careful care. You are very important --

*Mr. Upton. I am drinking lots of liquid --

*Ms. Eshoo. -- to all of us.

*Mr. Upton. It is my first Saint Patty's Day without a Guinness, ever. So --

[Laughter.]

*Ms. Eshoo. You can't have a Guinness when you have COVID?

*Mr. Upton. I am not having a Guinness, although they say that is healthy. It is good for your heart. I am not going to take that advice today.

*Ms. Eshoo. I would take a few sips --

[Laughter.]

*Ms. Eshoo. -- Fred. Okay, we are not going to penalize you for the time we are gabbing, so --

*Mr. Upton. All right, yes, I am --

*Ms. Eshoo. Let's set the clock for five.

*Mr. Upton. We have three seconds left on the clock.

*Ms. Eshoo. There you go. No, no, there you go.

*Mr. Upton. All right. Well, thank you. Madam Chair, I want to thank you for your commitment on this. I want to thank Chairman Pallone, but also my Republican colleagues, certainly, Mr. Guthrie and Cathy McMorris Rodgers, my seatmate, who I can't be next to as we confer this morning. There is probably not more an important issue on the health side than what we are dealing with today. So I really appreciate this hearing, the input of all the members as we work together to try and solve these diseases that impact virtually every single family pretty much every day.

And we need to move on and improve on what we were able to do as a committee when I chaired it back in 2016 with 21st Century Cures, when everyone, every member of this committee, 53 to nothing, supported that bill. And we now need to take advantage of that time and what we have learned to move forward.

So my staff reports that they have received legislative feedback from both the majority and the minority. We -- while I have yet to actually sit down and look at the review

since I came back this week, we look forward in the coming days to working with everybody to make sure that Cures 2.0 becomes law. And I want to thank again everybody in the hard-working staffs.

Real-world evidence, there has been a little talk about that earlier in some of the questions. We know that COVID has taught this Congress a very valuable lesson. And when the chips are down, the agency can work quickly and efficiently in support of product approvals, as we saw.

We also know that real-world evidence, or as -- we refer to it as RWE -- is going to help the agency improve its decision-making. According to the FDA's own website they quote, "This data holds potential to allow us to better design and conduct clinical trials and studies in the healthcare setting to answer the questions previously thought unfeasible.''

So for Dr. Allen with Friends of Cancer Research, Cures 2.0 includes provisions encouraging greater use of RWE to solve for the medical product development and approval problems of today. I would appreciate your thoughts on, one, whether we are utilizing RWE appropriately as much as possible, and your thoughts about the provisions as we -- and Chairman DeGette and I introduced 2.0 in that legislation.

*Dr. Allen. Sure, and -- well, thank you for the question. And first and foremost, we wish you well in your

recovery.

In terms of the utilization of real-world evidence, I think Dr. Ram highlighted some important points, that there still are methodological advancements that are needed in order to use electronic health data regularly for causal inference around the effect of a drug.

But I do think we also should note that the use of real-world evidence is not necessarily a new concept. It has played a very important role in things like monitoring for drug safety and identification of adverse events, hopefully earlier, when they can be mitigated, and well understood, and further characterized through subsequent study.

And also in looking at generating evidence about populations that weren't included in clinical trials, and there is a very important role for real-world evidence in the continued advancement of those methodologies to help augment clinical studies and, actually, can help advance the goals of many of the bills that are being considered today around diversity and inclusion in clinical research.

*Mr. Upton. Well, thank you.

Dr. Esham, I would like to just ask you quickly about the PASTEUR Act, which, again, we included in Cures 2.0. It is going to address, as you know, the problems of drug-resistant bacteria and fungal infections by encouraging new drug development.

This bipartisan bill -- a separate bill, the FORWARD Act, authored by Representatives McCarthy and Schweikert, would, in addition, improve research in the FDA's focus on fungal drug development.

If the goal of Congress was to prevent future pandemics from happening, how would the PASTEUR Act help Congress achieve them?

*Dr. Esham. Thank you. So again, we are very supportive of the provisions in the Cures that reinforces the importance of PASTEUR.

As you know, this is one of the leading -- antimicrobial resistance is one of the leading causes of deaths globally. Development for treatments for antimicrobial resistance do have unique challenges. And we definitely urge enactment and passage of PASTEUR this year to ensure that those policies are enacted that will drive and sustain much-needed investment in this space.

*Mr. Upton. Well, thank you. And in my closing seconds I would ask unanimous consent to enter into the record a letter signed by over 100 entities calling for the swift passage of the PASTEUR and FORWARD Act.

So with that, Madam Chair, I yield back the balance of my time. Go Blue.

*Ms. Eshoo. So ordered, so ordered.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. And please take careful care of yourself, you are special to all of us, Fred. And we will see you soon. How is that?

*Mr. Upton. I hope so.

*Ms. Eshoo. Great. Okay, it is a pleasure to recognize the gentlewoman from California, Ms. Matsui, for your five minutes.

*Ms. Matsui. Thank you very much, Madam Chair. And I want to thank the witnesses for being here today with us.

In recent years, Congress's work with the FDA, patients, and stakeholders has spurred the development of robust and meaningful patient experience data being submitted to the FDA for review, including as part of new drug applications. And one way to continue this momentum is to ensure there is clarity around whether and how the FDA uses this patient experience data.

To address this gap, I introduced the BENEFIT Act with bipartisan support from my colleague on the Ways and Means Committee, Representative Brad Wenstrup.

Importantly, I want to clarify that we are not proposing to change the FDA review process, or ask how the patient experience data influence a specific review decision. Rather, the BENEFIT Act was simply to have FDA describe if they receive patient experience data, and how it was incorporated in the review process.

Dr. Esham, BIO has been supportive of elevating the patient voice in the drug development process and, in fact, wrote a white paper explicitly suggesting that patient experience data be incorporated in the FDA benefit risk assessment, which my bill would promote.

Now, FDA does currently indicate whether or not it received submitted patient experience data. Dr. Esham, to your knowledge, does FDA ever then indicate what they do with that data? How might that insight be helpful to sponsors and patient organizations? Dr. Esham?

*Dr. Esham. Thank you, yes. And as you noted, you know, the 21st Century Cures Act, you know, required the FDA to make public about when patient experience data was considered in the approval of medicine. And over the years we have been working very closely with patient groups to better ensure that that information is more valuable and informative. And we do have a white paper we would be happy to share with you and your office.

We do think it is -- it has been helpful, with the recent publication that FDA published relating to the role of patient experience data and benefit risk analysis, and how to collect such information.

But we are supportive of your legislative efforts to promote the inclusion of patient experience data in the benefit risk assessment, and look forward to continuing to

work with you on this important issue.

*Ms. Matsui. Thank you.

And Madam Chair, I would like to submit for the record a stakeholder letter in support of H.R. 4472, as well as a BIO white paper and a report commissioned by the FDA on the use of patient [inaudible] data.

*Ms. Eshoo. So ordered.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Matsui. Thank you. Accelerated approval can be a critical tool for getting novel medication to market faster, especially for rare disease patients who often lack access to any FDA-approved treatment options.

Chairman Pallone's accelerated approval bill makes changes to the timing and transparency protocols for post-approval studies used to confirm a product's clinical benefit. Dr. Ramachandran -- I hope I didn't -- I hope that --

*Dr. Ramachandran. That is okay.

*Ms. Matsui. Okay. Why are these proposed reforms to confirmatory trials beneficial for rare disease patients?

*Dr. Ramachandran. Yes. Thank you so much, Congresswoman, for the question.

You know, the proposed reforms within Chairman Pallone's Accelerated Approval and Integrity Act are critical for rare disease patients, one, to be able to show and demonstrate very clearly that these drugs that are being approved much more quickly and made available to patients much more quickly are actually truly clinically beneficial.

You know, a lot of the statements have been around speed, and how quickly, you know, these drugs are coming to market, how quickly they are getting converted to traditional approval. And when we actually looked at the data to see how long these trials take to actually show any sort of result,

they only take about 17 months. So the provisions within Chairman Pallone's bill to have automatic expiration after one year or five years after a drug has come to market are perfectly reasonable, and kind of give even more ample time for manufacturers to meet these requirements.

But mostly for me, as a clinician, I just want to know for sure that the drug actually works, and these post-approval studies without adequate oversight won't show that unless the FDA is keeping an eye on them.

*Ms. Matsui. Sure. Absolutely. Well, thank you so much.

Now, lastly, I have heard concerns that the accelerated approvals will automatically expire in the middle of clinical trials if we pass the Accelerated Approval Integrity Act. But as I understand the bill, this acts as a backstop, and FDA will allow clinical trials to continue beyond five years if they are making adequate progress. Dr. Ramachandran, [inaudible] Accelerated Approval Integrity Act build in this flexibility?

*Dr. Ramachandran. Yes. The flexibility that is built in is really for the FDA to, you know, understand that, you know, different drugs and different diseases might require different periods of time. And so, as a part of the bill, the FDA does negotiate with the sponsor, and does discuss with them what a appropriate completion date would be for

those post-approval studies.

And hopefully, you know, that builds in that FDA flexibility to be able to say, okay, a trial might take longer than the five years, that we have the automatic expiration, and the sponsor can continue to engage with the FDA to not have the drug withdrawn if it is in the middle of a trial.

*Ms. Matsui. Well, thank you so much. I appreciate the clarification, and I yield back.

*Ms. Eshoo. The gentlewoman yields back. It is a pleasure to recognize the gentleman from Virginia, Mr. Griffith, for your five minutes of questions.

*Mr. Griffith. Thank you very much, Madam Chairman. I appreciate it. Let me dovetail a little bit with Representative Matsui.

We had a discussion last week during the user fee hearing -- I -- sorry, February 3rd, last month, related to risk evaluation and mitigation strategies for clozapine and another drug that -- its name is hard for me to pronounce. And I just want to make sure, Madam Chair, that we are working on this issue. Dr. Joyce, Representative Matsui, Barragan, and I are all working on some legislation we hope to have coming out that will help on this.

But as you will recall, we learned that physicians, pharmacists, and patients lost access to the REMS platforms

for these drugs when new platforms were launched late last year. And our legislation is intended to provide more accountability and transparency so the patient doesn't find themself suddenly without the medicine that they have relied on and need. So I will leave that part at that point, but I did want to dovetail with Representative Matsui and her work on those areas.

*Ms. Eshoo. So noted.

*Mr. Griffith. Thank you.

Mr. Gaugh, I want to thank you for your written testimony and your support of the INSPECTIONS Act, which is H.R. 7006, which Mr. Welch and I introduced in an effort to improve FDA's inspections of foreign drug manufacturing establishments. This committee has heard many stories, some of them, frankly, horrific, about the conditions and the shortfalls of our -- the conditions in foreign labs or foreign medicine-producing facilities, and our shortfalls of current inspection processes. And it is time that we start addressing them.

You say in your written testimony that my bill could be strengthened -- and that is always a good thing, you always want to learn what you can do better -- with additional provisions on the use of alternatives to in-person inspections. And I would first like to clarify. You say the FDA should be required to evaluate these tools when an

in-person inspection is not possible, but then go on to describe a situation in which an in-person inspection does occur.

In the first instance, are you describing a situation in which an in-person inspection may be temporarily impossible, but later resolved?

*Mr. Gaugh. Yes, that is correct.

*Mr. Griffith. Okay, and I suspected that was the case.

The GAO report required by the bill that Mr. Welch and I put in would require a thorough description of all the alternative tools, including remote inspections other trusted countries are utilizing to facilitate inspections of foreign establishments. Could you briefly describe to the folks at home how a remote inspection works?

*Mr. Gaugh. So remote inspection -- and it is not an inspection, it is an evaluation. So as the FDA has very eloquently said, it is a remote evaluation, RIE. And what they do is a virtual inspection, if you will, but it is not inspection. Based on the legislation, and how the legislation in 704 is written, it can't be an inspection, but it still does virtually the same thing.

In fact, there was just an article in Pink Sheet this week that talked about -- that the FDA talked about how they are doing these inspections. They want to make sure that the facilities have the right equipment, so they can walk around

with an iPad or a very high-level iPhone to be able to look at the different areas that they are inspecting. So they will have the papers in front of them, the FDA will, at their desk. Then they want to do a walk-around to see if the SOPs that they are reading and the actions are equal.

*Mr. Griffith. And that equipment is paid for by the manufacturing facility, is it not? The smartphone or the laptop.

*Mr. Gaugh. Yes.

*Mr. Griffith. Yes. And you know, I have just got to say, obviously, somebody live and in person is going to be better. But when we don't have enough inspectors -- and we are already way behind in inspecting some of these facilities, whether they be in Europe or particularly in Asia -- this is better than nothing.

I mean, we heard testimony in one of the inspections that they actually found feces on the walls in the areas where they were manufacturing medicines that we are taking. And so at least this would show that. And even if they cleaned it up just for that day, that is better than not having anybody there. Isn't that true?

*Mr. Gaugh. That is correct, yes. So it is not as good as in-person, because you may only see three of the four walls, for example, and the fourth is the one you are concerned about. But in today's world, where we are not able

to inspect, or the FDA says they are not able to inspect, we need to have another tool, and this is a very viable tool.

*Mr. Griffith. I appreciate it very much, thank you.

Dr. Esham, you were talking earlier, and you got into resistant microbials to our antibiotics, and I am sure you all are looking into it. And I would encourage everybody to take a look at "The Perfect Predator.'' It is a book that I read about a year-and-a-half ago, and it is by Steffanie Strathdee and Thomas Patterson. And it is about -- it is actually a love story with medical science all thrown into it. It is a great read, but it talks about phage therapy, and what we ought to be doing, and where we ought to be going. And I think that is a great tool for us in the future. Would you agree, yes or no?

*Dr. Esham. Yes, and I am excited to have a new book to read.

[Laughter.]

*Mr. Griffith. There you go. I yield back.

*Ms. Eshoo. A good answer. It is a pleasure to have her right here in the chamber, the gentlewoman from Florida, Ms. Castor, for your five minutes.

*Ms. Castor. Well, thank you, Chair Eshoo, for calling this very important hearing. And thank you to all the witnesses for being here today.

As we discuss innovation in medicine, it is critical

that innovation is accessible to all. And many of the bills being considered today address diversity and equity in the biopharmaceutical development process, and I look forward to working with the chair to enact them.

However, there is an important population that also must be considered in any effort to advance innovation, and that is pregnant and lactating people. Each year in the U.S., six million women become pregnant, and more than three million initiate breastfeeding. Almost 90 percent of women in the U.S. will give birth during their lifetime. And despite how common it is, and how important, how critical that time of pregnancy and postpartum is to development of mothers and -- for mothers and the development of babies, there is very little information on the safety of therapeutics and vaccines in pregnancy, and even less on safety for the baby while breastfeeding.

And we saw this failure most recently during COVID-19, with the vaccine there, where developers originally chose to exclude pregnant people from their trials, leading many pregnant people, who are at higher risk for severe illness or death, to forgo protection of the vaccines. So we can't let the status quo persist.

I was proud to sponsor legislation that was included in the 21st Century Cures Act that created the PRGLAC Task Force, which issued 15 recommendations and a detailed

implementation plan to ensure we protect pregnant and lactating people through research, not from it. And I am working now on follow-up legislation to advance many of these recommendations.

So, Dr. Esham, many of the PRGLAC recommendations focus on enhancing post-market surveillance for the therapies and vaccines in pregnancy. And I was encouraged to see a section on pregnancy safety in the PDUFA commitment letter. Can you explain why current pregnant safety surveillance systems haven't produced robust data, and describe the opportunities to strengthen pregnancy registries and other post-market studies for pregnant and lactating people?

*Dr. Esham. Well, I think you actually very eloquently laid out that -- some of the issues that we were trying to resolve through the PDUFA 7 agreement. Again, as you stated, there is a section in there to really try to advance how -- you know, to require FDA to develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used.

So again, we think that the provisions in PDUFA 7 will be very helpful, and I am happy to discuss that with you in detail.

*Ms. Castor. Great. Dr. Ramachandran, experts advise that we need focused research to assess the risks of medications to expectant mothers and babies. How does

industry and the research community approach inclusion of these populations in clinical trials and research?

And what more can trial sponsors do to ensure pregnant and lactating people are represented in clinical trials?

And would clearer guidance from the FDA, with more specific recommendations for trial sponsors on the inclusion of these populations be helpful?

And what other steps do you think we should take?

*Dr. Ramachandran. Yes. Thank you so much for this question. This is a question that is very near and dear to me. I am actually a family medicine physician by training. I take care of babies, kids, pregnant women, and older adults. So it is a question that has come up routinely, especially when talking about COVID-19 vaccines. I was actually breastfeeding when I received my vaccination, so it was a key consideration for me, as well.

You know, currently, clinical trials or industry sponsors tend to not include pregnant or lactating women as a part of the studies. Part of this is in trying to include populations that are healthier, that are populations without comorbidities or any other underlying conditions to be able to better tailor results to be positive. And that has been an unfortunate consequence in terms of FDA oversight on inclusion and exclusion criteria.

However, I am, you know, reassured that, because of your

legislation and with what is included PDUFA 7, that there will be more post-marketing surveillance, and more opportunities for registries, observational data of pregnant women, so that we can be able -- pregnant and lactating women -- so we can be able to know what the effects are on those populations.

But definitely, clear FDA guidance on this issue is critically important, and this is an area in particular where FDA could actually put out guidance regarding real-world evidence in the post-marketing surveillance phase, in particular, for these populations. That would be very beneficial for us, as practicing clinicians, to be able to offer guidance for our patients.

*Ms. Castor. Thank you very much.

Thank you very much, Madam Chair, and I will yield back my time.

*Ms. Eshoo. The gentlewoman yields back. The gentleman from Florida, Mr. Bilirakis.

There you are.

*Mr. Bilirakis. Thank you.

*Ms. Eshoo. You are recognized for your five minutes.

*Mr. Bilirakis. Thank you, Madam Chair --

*Ms. Eshoo. Good to see you.

*Mr. Bilirakis. -- I appreciate it very much, and I want to thank the witnesses for --

*Ms. Eshoo. And his father -- for those that may not know this, Mr. Bilirakis's father at one time was the chairman of this subcommittee, a wonderful chairman.

*Mr. Bilirakis. Yes, yes, 10 years. Ten years, yes. Thank you very much for bringing that up. He is doing great. Thank you.

I am particularly grateful to see my bill, Madam Chair, and I appreciate you putting it on the agenda today among the 22 bills. I co-lead this bill with the caucus chair, Representative Butterfield, the Rare Disease Caucus, and it is called the Speeding Therapy Access Today Act, the STAT Act, H.R. 1730 on the docket today. And I am hopeful the chair will continue to work with us, and I know she will, on this bipartisan bill to consider it as part of our user fee package. I know there are no guarantees.

I have said before rare diseases are not a rare problem, and they affect almost 1 in 10 people in our nation. And while we have made great strides and progress in the development of therapies for certain rare diseases, we have a long way to go. And there are particularly -- particular challenges with these small patient populations with up to 95 percent of rare conditions that still do not have an approved treatment, especially for ultra-rare diseases. We have got to do something about that.

So Dr. Vereshchagina and Dr. Esham, can you share some

thoughts on why it is so difficult to develop treatments for the rare disease in ultra-rare disease communities?

And what ways could cross-agency approach, that kind of an approach at FDA, help solve some of the challenges you described?

*Dr. Vereshchagina. Thank you for this question. And as I mentioned in PhRMA's opening statement, we recognize rare disease drug development as an area that still requires a lot of attention.

And as you mentioned, many patients still lack FDA-approved treatments. So there is a lot of challenges stemming from the fact that patient populations are very small, and it might be challenging to recruit patients into clinical trials. And this becomes even more of a concern for ultra-rare diseases, where patient populations can be, you know, literally, in dozens or even less.

And because of small patient populations, there is also a challenge of, you know, sometimes natural history of disease is not known. Today already many people mentioned maybe there are not established endpoints.

So this is why we supported rare disease drug development provisions in PDUFA, both the current cycle and the upcoming PDUFA 7 cycle. It includes dedicated pilot to work on establishing and finding those endpoints for disease drug development.

It also includes provisions specifically supporting FDA's task forces in both drug center, CDER, and biologics center, CBER. So a sponsor will be able to continue working with FDA very closely on solving those underlying clinical trial design and endpoints issues.

*Mr. Bilirakis. Thank you.

Dr. Esham, do you have anything briefly to add, please?

*Dr. Esham. I think she stated it very well. Again, these are issues that -- the challenge is compounded by often working where there is little precedence. This is innovation in its truest form.

You know, as you know, there is -- thousands of diseases still don't have a treatment available, and there is thousands more diagnosed every year. So again, we need to foster development pathways for the treatments of these diseases, particularly for those patients that have no options.

So we would love to continue to work with you on these --

*Mr. Bilirakis. Thank you.

*Dr. Esham. -- important issues.

*Mr. Bilirakis. Thank you so much. I appreciate it.

Dr. Vereshchagina -- I practiced this, but it is very difficult; I have a tough name, as well -- so your testimony also specifically mentioned the need to preserve incentives

for rare disease drug development, such as those under the Orphan Drug Act, for continued research and development investments. I couldn't agree more.

I truly believe that the STAT Act will continue to enhance those incentives by bringing in additional cooperation and expertise within the FDA to treat rare conditions, such as advancements in trial design, statistical analysis, and regulatory science.

Can you explain how new incentives and tools at FDA could work to help bring rare disease products to market faster?

*Dr. Vereshchagina. Yes. Thank you for this question. So the Orphan Drug Act demonstrated that it has been tremendously helpful for companies to provide that needed incentive to go into the area of a lot of uncertainty. And maybe there is -- where, again, there is not enough scientific data available, and the basis. So companies do need those incentives and regulatory predictability to go into those areas and develop much-needed drugs for rare diseases.

And while I can't specifically comment on the STAT Act, PrRMA and our member companies do support incentives for rare disease drug development.

*Mr. Bilirakis. Thank you very much.

I yield back, Madam Chair. Thank you.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentleman from Maryland, Mr. Sarbanes, for your five minutes questions.

*Mr. Sarbanes. Madam Chair, thank you very much for the hearing today, and I want to thank our witnesses, for sure.

The purpose of the hearing is to discuss how we streamline the development and approval process for drugs and therapeutics, as well as how to strengthen program integrity, with the goal of ultimately getting people across the country the medication and therapies they need to live long and healthy lives. Obviously, we have got a number of different proposals that are on the table and in front of us today.

Accomplishing this broad goal will not be a small feat. We know that. In order to achieve important biomedical breakthroughs that will make this goal a reality, we need to diversify the kinds of research being conducted in the field of biomedicine. Many people have spoken to that.

A critical component of this, I think, is to make sure that we are supporting early career researchers. We know that competition for Federal research dollars is fierce, and NIH can only support a certain percentage of the projects that it believes are qualified for funding. So it is a tough environment, competitive environment.

Early career researchers who have not yet had a chance to establish a track record of research success are,

obviously, at a disadvantage when competing with their more established peers for these limited funds. This means that we may not only miss out on important and perhaps novel research that may -- that they may choose to pursue, but also face an inadequate pipeline of experienced researchers to fill the void where more established -- when more established researchers retire.

Dr. Mesa, can you speak to the specific benefits that funding early career researchers can bring in this space?

*Dr. Mesa. Thank you very much for the question. It really is a critical piece.

As a cancer center director, part of my role is helping develop folks, really, from the high school level all the way through junior faculty to pursue careers in cancer, and to make a difference. You know, and the ability to be able to support them is critical, both with Federal programs as well as a variety of innovative approaches that are being taken with everything from colleagues in the pharmaceutical industry to independent foundations.

But it really is critical. They have to have that initial opportunity to be able to bring their talents to the critical questions that we have heard today in front of the committee. Whether it be rare diseases, cancer, or diversity, we need that intellectual firepower working on our behalf.

*Mr. Sarbanes. Another way -- thank you very much, I appreciate for that (sic). Another way to diversify biomedical research, if this makes sense, is to cultivate more diversity among the scientists that are conducting that research. And according to the National Science Board's Vision 2030 Report, which discusses what the United States should do to stay a global leader in innovation, women and minorities continue to be under-represented in science and engineering.

Again, to you, Dr. Mesa, what steps can be taken to help increase diversity among researchers in the field of biomedical research?

*Dr. Mesa. It truly is about every stage of the pipeline.

So at our university it even begins at the high school level, really trying to develop health care careers, and have pipelines that then lead through the undergraduate level, graduate programs, and really programs to be able to establish them as junior faculty. So the development along the whole pipeline is really critical.

If it is just at the junior faculty level, we probably don't have the diversity yet. As an NCI-designated cancer center, we now all have been asked, very appropriately, to have diversity, equity, and inclusion plans in place for our centers to really try to develop both our workforce and our

leadership for the future.

*Mr. Sarbanes. Thank you. And of course, we know, you know, these diversity initiatives, wherever they exist, can either become just sort of box-checking exercises, or they can become a sort of leading, vibrant edge of whatever the organization is. And that is, obviously, what we are looking for in the research space.

Dr. Esham, I would like to turn to you briefly on these two questions: What role can industry play in supporting early career researchers and increasing the diversity of biomedical researchers?

*Dr. Esham. Thank you. I think we do have the opportunity to play a role. And again, I think, as mentioned, we often try to and are continuing to establish collaborations to communicate at the earliest levels what the possibilities are in having a scientific and health-driven career.

We work with many of our state affiliates that engage with high schools, middle schools. Many of our companies often engage with high schools and middle schools to -- again, it is about showing the opportunity.

You know, I could speak -- I grew up at a small town in Kentucky, and I myself was not aware of these opportunities. I sort of accidentally -- and thankfully -- stumbled into many of them.

But providing children of all races and genders the ability to properly assess what their opportunities really are is quite important.

*Mr. Sarbanes. Thank you very much.

I yield back, Madam Chair.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentleman from Florida, Dr. Dunn, for your five minutes of question, sir.

*Mr. Dunn. Thank you. Thank you very much, Madam Chair and Ranking Member Guthrie, for hosting this hearing today to discuss legislation that may very well impact development of future cures.

As we consider the policy that may accompany the user fee agreements this year, it is important to strike a balance between the FDA giving it the regulatory tools it needs to ensure quality and safety, while still guaranteeing that the agency doesn't get in the way of the American innovation that we are all so proud of.

Congress must also continue to work to ensure that patients have access to those medications soon after they are approved. And this involves some forward-thinking, accelerated approval processes such as Ranking Member Rodgers's Accelerating Access for Patients Act, which I intend to support.

I also want to convey my support for H.R. 1730,

introduced by Representatives Bilirakis and Butterfield, which aims to move the needle on rare diseases; and H.R. 4511, introduced by Dr. Burgess to, importantly, bring real-world evidence into the review process.

Another component of guaranteeing access to patients is supporting the development of generics and biosimilars, specifically the interchangeable biosimilars, which should be more affordable and, therefore, more easily accessed by patients.

When the FDA testified in front of this committee last month, I asked about their willingness to provide the drug sponsors with comprehensive FDA review documents in the event they hand down a Complete Response Letter to an applicant. The FDA answered that this requirement would have a chilling effect on the review process. Frankly, that answer frustrates me.

As we all know, new drug sponsors spend years and years, tens of millions of dollars to develop a single cure, and often they fail along the way. So when an innovator finally does file for FDA approval, meets the FDA's surrogate endpoints, and their product has no evidence safety concerns, and then still receives a Complete Response Letter, I believe they should be granted access to the comprehensive review documents that went into that decision. This type of transparency would help them remedy any deficiency, and would

also provide certainty to the investors. And this is really important for a lot of small and mid-sized biotech companies who find themselves in this position, and then are forced to actually shut down because of that.

So to that end, Dr. Esham, a recent report from Pink Sheet detailed an uptick in the issuance of CRLs compared to previous years. Could you speak to the issue of Complete Response Letters lacking comprehensive information about application deficiencies, and how does that hurt you?

*Dr. Esham. Thank you for that question. And I have read the article.

I will say, in conversations with our member companies, it is important that when -- it is critical, when receiving a CRL, that the information provided clearly defines what the issues or deficiencies were that led to that decision. Without that information, it is very difficult to determine whether those hurdles can be overcome and investment is warranted to conduct additional studies or not.

And the problem is not whether treatment fails because it did not meet regulatory standards to support approval. It is whether the development is halted of a treatment that may provide benefits that we want to avoid.

*Mr. Dunn. Yes, so I am not surprised to hear that. Thank you very much.

Dr. Vereshchagina, the -- how does a sponsor, drug

sponsor, approach their decision-making after a CRL is issued and calls for new clinical trials, despite hitting previously agreed-upon endpoints?

*Dr. Vereshchagina. Thank you --

*Mr. Dunn. So you know that happens, right?

*Dr. Vereshchagina. Yes, and I think the most important thing highlight here is the open communication between sponsors and FDA that Complete Response Letters are not surprised. And this is, for example, why user fee agreements include specific opportunities and multiple points during the drug development that requires FDA and sponsors get together and discuss this issue.

So it does not actually get to the point of the Complete Response Letter because, as you said, it may impact clinical development. But the goal is really to make sure that there is very clear understanding on both sides what is required for the timely approval, and that sponsors and FDA is together working --

*Mr. Dunn. So being -- my time is -- I am going to say to sum up, it sounds like you two are in agreement that clearer communication between the drug sponsors and the FDA throughout the process, including at the time of the CRL, but before that as well, it would be imperative to actually help us innovate and create new drugs for Americans.

So thank you very much, Madam Chair. I yield back.

*Ms. Eshoo. The gentleman yields back. It is a pleasure to recognize the gentleman from Oregon, Mr. Schrader, who has been participating, sitting here, and listening, and has been very patient.

You have your five minutes now.

*Mr. Schrader. Thank you, Madam Chair, I appreciate it. I would like to thank everybody for being here for the conversation, very important conversation on innovation and ability to improve getting medications, lifesaving devices to the marketplace. I would like to discuss my biosimilar interchangeability bill.

When the -- when we all worked on the Biologic Price Competition Innovation Act, we laid out a process, set a pretty high bar for interchangeability, given the relative newness of the -- of these products. And for that accomplishment we set a finite amount of exclusivity for the first such interchangeable biosimilar with a single biologic reference product.

Unfortunately, since that time, FDA has changed the original intent of the Act, and interpreted it so that a component of determining the eligibility, the strength of two products, to mean the same exact content with the same exact concentration of the biosimilar. Sometimes that is important, but in many cases it is not.

For example, within the current interpretation, a half mil of an active ingredient as formulated in a one mil solution is considered lower concentration, compared to a half mil in a 1.75 mil solution. Both contain the exact same amount of active ingredient, slightly different levels of inactive saline, but the latter is considered high concentration based on the ratio. No clinical difference in the outcome of that product.

What happens under that scenario is that the reference product sponsor can block biosimilar -- generic, if you will -- competition by making clinically insignificant changes to product concentration. That was never the intent. The goal was to get biosimilars, you know, generics to marketplace as quickly as possible, and reward innovation, reward actual innovation.

I am floored by the assumption that some in the industry seem to think that making that exclusive change, you know, for different concentrations would be a legitimate exercise. It goes against everything Congress has stood for, myself in particular, trying to get generics to marketplace.

So I guess a question. Dr. Gaugh, I go to you. Has the FDA awarded exclusivity for interchangeability on two different biosimilars for different concentrations? Where are we with that?

*Mr. Gaugh. Yes, they have done that. That is correct.

*Mr. Schrader. And what has been the effect of that, in your opinion, with regard to the ability to bring different generic products, different biosimilars to the marketplace?

*Mr. Gaugh. Thanks for the question, and thanks for the bill that you put forward.

We totally support the concept of where you are going with this bill. The concern is we think it may have some unintended consequences on really opening back up BPCIA completely, and could lead to some other exclusivity issues that might occur.

So we would like to have the opportunity to work with you to maybe tweak this a little bit further, because there is still that exclusivity period that we are concerned about.

*Mr. Schrader. Yes, we definitely want to protect that exclusivity period for those folks that are bringing it in. I would be glad to work with you on that. And that is part of the reason we still have the waiver ability for FDA, to make sure that -- because sometimes -- I am a veterinarian in the real world, and concentration does matter in some cases, and so we need to have a little leeway with the FDA to be able to pursue that.

Second question, I guess it would be for Dr. Esham. I am also very interested in the FDA Modernization Act. I think that has some great opportunities out there. As a veterinarian, you know, any testing that can be done without

the use of our four-footed animal friends, I think, is to our advantage, and certainly to their advantage.

Precision medicine, using tissue cultures and some of the advanced techniques that I think we are looking at here in the 21st century is pretty darn exciting. I wish we had that when I was in active practice. However, I think it is also important to recognize that, beyond tissue culture and, you know, computer modeling, there are complex inner physiological interactions within the animal and human body that need to be taken into account.

So I just want to, you know, set people's concerns -- or allay people's concerns, hopefully. I am a fan of the legislation. Is there any mandate in the legislation that FDA must only use non-animal techniques and evaluations to determine whether a drug is safe?

Yes, ma'am.

*Dr. Esham. Oh, sorry. I will point out that we are still reviewing this legislation, and definitely want to get back to you and continue to work with you on this issue.

I will also state for the record that BIO is committed to advancing tools and methodologies that can be alternates to animal testing.

*Mr. Schrader. Good.

*Dr. Esham. We even have some peer-reviewed papers on alternative approaches to non-human primates. So again, I am

happy to come in and have more detailed discussions with you.

*Mr. Schrader. So how do you see that working out? I mean, it is pretty exciting, having alternate models out there, something the old model is based on what we did in the 1930s, where we had no alternatives. So this offers, I think, some pretty exciting new -- how do you see that playing into, you know, drug evaluation going forward?

*Dr. Esham. I think we need to continue to advance it and make it, you know, as much as we can, make it more -- an approach that can be used in drug development. Again, we are not in an either/or situation, but we need to continue to advance these alternatives.

*Mr. Schrader. Very good. And I yield back. Thank you very much.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentleman from Utah, Mr. Curtis, your five minutes of questions.

*Mr. Curtis. Thank you, Madam Chair. Thank you, Mr. Ranking Member. Thank you, witnesses.

I add my voice to that of my colleagues, which seems to be a strong bipartisan theme that the policies that we are considering alongside the user fees should ensure that the FDA is functioning well and efficiently, and keeping up with the vast needs.

It is imperative in Utah and, really, for all Americans

that timely access to safe and effective lifesaving medical products is something that they can look forward to. I think, if we can foster American innovation, and if the FDA can keep up, we can do great things with the scientific advancements.

I have spoken at previous hearings about the importance of FDA initiatives that advance the development and access to treatments that fulfill unmet needs. I think, in this hearing room, we have heard some passionate testimony from some of our witnesses about the unmet needs, and how it impacts their lives. I am proud of the bill that I helped champion, and it is being considered today: the Equity in Neuroscience and Alzheimer's Clinical Trials, ENACT, Act, which would encourage the use of remote health technologies, such as remote patient monitoring, to ease the burden of participation for many communities.

My district in Utah -- many people hear me talk about this a lot -- is very rural. I actually have 400 miles from top to bottom, and I understand the amount of time people must spend traveling to a clinical trial site creates significant challenges. Geographic limitations should not impede progress when there are technologies available that will help us increase participation of unrepresented populations in clinical trials. As technology advances, I believe we will continue to find ways to utilize such

advancements to improve our health care system and the medical products on the market.

I think one place we can do this is how we provide pharmacists and physicians with prescribing information. One option we should consider to do this is electronic billing. Dr. Vereshchagina -- we have all tried to pronounce that, and I appreciate your patience with us -- you highlighted the importance of digital health technologies. Can you tell us what role you believe electronic labeling plays in ensuring physicians and pharmacists have the most up-to-date prescribing information?

*Dr. Vereshchagina. Thank you for this question, and thank you for recognizing the value that digital technologies can bring to both drug development, but also to healthcare.

As the response to COVID-19 pandemic indicate that there is tremendous potential in both collecting data, analyzing data, sharing data electronically, both in clinical trials and in patient care settings. So that is an area that biopharmaceutical industry and our member companies are definitely very interested in, excited, and supportive. And we included specific provisions in PDUFA 7 agreement to make sure that we continue to develop methodologies, and that data is being able to be collected and analyzed and used for regulatory decision-making.

*Mr. Curtis. Thank you.

Still on the topic of digital health technologies, Dr. Esham, I saw you nod your head when I was talking about these distances, dealing with participation in clinical trials. Could increasing remote health technologies in clinical trials support expediting trials' responsibility and certain solutions, and what should we be looking at in that area?

*Dr. Esham. Absolutely. We do believe that the use of telehealth and other digital technologies can reduce patient burdens generally, and also break down some of those prohibitive geographical barriers by lessening the amount of time a patient needs to visit a clinic in person that requires taking off work, finding child care.

These technologies also enable the ability to capture data in a less obtrusive manner, and in a more continuous manner, and enable staff to potentially engage with patients more effectively and also in a more timely manner.

So it does, can, and should play a significant role, because we do believe it will make participation and can make participation more manageable for patients.

*Mr. Curtis. Thank you. Like my colleagues, and all of you, I believe it is important to advocate for reduced out-of-pocket costs for pharmaceutical drugs for our patients. One option to consider is the low of -- is the role of low-cost, generic, and biosimilar medicines in our pharmaceutical market.

That said, we should also be mindful that it is not FDA's job or place, or even legal for them to set these prices. Dr. Gaugh, what role does FDA play in ensuring a competitive, generic, and biosimilars marketplace that will ultimately drive down the cost of these drugs for the American people?

*Mr. Gaugh. I think the role they play is through what we have accomplished in both GDUFA and BsUFA, and that is access to the affordable drugs.

So through both user fee programs we have set up milestones, if you will, and metrics that the FDA must meet for the review of applications -- not necessarily the approval, but the review -- within a 10-month timeframe. And we have also added in GDUFA a two-month add-on timeframe. If a product is determined an imminent approval product, but something needs to be fixed, something very slight, there is an additional two months that is added in. So it turns into a 12-month clock, yes. But had that not happened, it would have been a Complete Response Letter, and would have gone into a second cycle, and it would have been many months afterwards.

So it is really that timeline that we have improved from years ago, when GDUFA didn't exist, at a 48 to 50-month time point for approval to today, where we are at about a 27 average --

*Mr. Curtis. Thank you. Yes, thank you. Thank you to our witnesses.

Madam Chair, I yield my 13 seconds back.

*Ms. Eshoo. There you go, thank you. Thank you very much, Mr. Curtis. And I always take note that, no matter how long a hearing is, you are here from beginning to end. And that says everything about you and your attention.

And Morgan, who is getting up and leaving now, too.

[Laughter.]

*Ms. Eshoo. And he didn't hear me, either. Okay. Well, you have to smile, right?

The chair is very pleased to recognize the gentlewoman from Illinois, Ms. Kelly, for your five minutes of questions.

*Ms. Kelly. Thank you, Madam Chair and Ranking Member Guthrie, for holding this very important hearing.

Madam Chair, I am glad that our bipartisan DEPICT Act has been included, which will require the FDA to incorporate accountability and enforcement mechanisms for clinical trial diversity. However, real progress on clinical trial diversity will require a multifaceted approach across Federal agencies.

Commitments from industry are simply not enough. We need to do better for patients of diverse demographic backgrounds. We need to have accountability for conducting clinical trials that are reflective of the patients impacted

by the disease or condition.

Dr. Ramachandran, thank you for supporting the accountability and enforcement mechanisms laid out in the DEPICT Act to ensure clinical trial diversity. Would there be any benefit to implementing similar accountability and enforcement measures at the NIH, such as requiring the sponsors that work with NIH to establish -- I am sorry -- your measurable diversity goals, and the funding application process, and have these goals be [inaudible] throughout the trial?

*Dr. Ramachandran. Thank you, Congressman, for the question.

And yes, definitely, there would definitely be benefit for NIH to set similar enrollment targets for sponsored trials or funded trials from the NIH. There is a couple of reasons for this.

The NIH is paying -- playing an increasing role in funding clinical trials, especially for a number of the novel gene therapies that we are seeing coming to market, and particularly those that are going to be effective or may be effective for communities of color. You know, sickle cell disease, for instance, there is a promising treatment that NIH is playing a critical role in advancing. And so making sure that those trials also include patients that are representative of the patients who will be prescribed this is

really important, not just for the patients, but also for us, as clinicians.

The other part of this, too, is that, you know, as the nation's medical research agency, we would hope that the trials that are funded by the NIH also reflect the nation's population. And so, you know, it is -- I find it very critical. And, you know, thank you for your leadership in terms of also making sure that there is a whole-of-government approach in terms of ensuring representation in clinical trials.

*Ms. Kelly. Thank you. My dear colleague and friend, Congressman Butterfield -- who, yes, we will miss greatly -- mentioned about our bill, the Clinical Trial Diversity Act, that will be introduced this month. And this would hold NIH-funded clinical trial sponsors accountable for working towards clinical trial diversity goals.

Diversity goals are not intended to be quotas. We do think there needs to be an enforcement mechanism. Our bill would empower NIH to use existing penalties, such as apply conditions of funding continuation or, in extreme cases, terminate funding.

Why is enforcement an important piece of holding clinical trial sponsors accountable for diversifying clinical trial participants?

*Dr. Ramachandran. Yes, thank you for the follow-up

question. And, you know, this is critically important because, basically, what isn't measured won't be managed.

So without NIH setting those sorts of targets, they are not -- there is not going to be movement from industry as we have seen over the past, you know, decade in terms of FDA trying to do non-enforceable measures to increase representation in clinical trials, and really not moving anywhere in terms of ensuring that more patients of color are being enrolled, and even, you know, regarding older adults being enrolled in these trials, as well.

On top of that, you know, NIH already does this to some extent. It has great success in terms of setting enforcement measures around clinical trials, particularly around clinical trial registration and results reporting that has led to industry sponsors paying attention, but also all trial sponsors paying attention and actually adhering to those requirements. And this benefits not only patients, but also, as clinicians, to really know how these drugs and these devices will actually affect our patients.

And with NIH playing such an important role in terms of catalyzing, you know, truly transformative innovation, we also want to make sure that they are being innovative in terms of making sure that trials are representative of the nation's population.

*Ms. Kelly. Thank you so much. And we are thrilled

Doctors for America has endorsed the Clinical Trial Diversity Act.

Dr. Mesa, would there be any benefit to requiring that NIH-funded clinical trials implement alternative follow-ups, such as phone or telehealth alternatives, or increasing the availability of night and weekend appointments?

*Dr. Mesa. Yes. Without question, clinical trials really are a critical aspect of how we care for difficult diseases, including cancer. And certainly having both, you know, Federal, as well as, you know, sponsored trials from the pharmaceutical industry really try to make the trials as patient-centered as possible is critical. So using new technologies, approaches, expanded hours -- really, think about what does it take to make it feasible for the patient.

*Ms. Kelly. Thank you so much. And I am pleased that Leukemia and Lymphoma Society has endorsed the Clinical Trial Diversity Act. This bipartisan bill, in conjunction with the DEPICT and DIVERSE Act, would ensure that there is accountability for clinical trial diversity, and that sponsors have the tools to meet diversity enrollment goals.

Thank you so much, and I yield back.

*Ms. Eshoo. The chair now recognizes the gentleman from Georgia, and he is coming in virtually for his five minutes of questions.

Hi, Mr. Carter.

*Mr. Carter. Thank you, Madam Chair.

*Ms. Eshoo. How are you feeling?

*Mr. Carter. I feel good. I feel good. Thank you for asking. I am --

*Ms. Eshoo. Good.

*Mr. Carter. I am out --

*Ms. Eshoo. I think we need to reset the clock, please.

*Mr. Carter. -- some time soon.

*Ms. Eshoo. Okay, great. There is your five minutes.

*Mr. Carter. Thank you, and thank all of you for being here, the panel members. I want to talk real quickly about my legislation, Enhanced Access to Affordable Medicines Act.

There was a recent GAO report that said that last-minute brand labeling changes were a factor that could potentially delay approval rates for generics. And, you know, approval rates for generics is something that concerns me very much. We give brand name drugs seven years for a patent. But, in reality, that 7 years is more like 10 or 12 years, because it takes so long to get a generic to market. And I am trying to do all that I can to speed that process up, so that we can get generics to market as soon as possible.

Congress attempted to address this. We attempted to address this problem in 2010, and -- but there are still gaps in implementation that have not been fixed with this problem.

The FDA has also stated that -- working overtime to

approve generic medicines, but that issue still exists, as well.

My legislation, the Enhanced Access to Affordable Medicines Act, would propose minor revisions to close the gaps to the existing law, and it would prevent last-minute brand labeling changes from further delaying generic entry.

Mr. Gaugh, I want to ask you. Are last-minute brand label changes still a problem?

*Mr. Gaugh. Thank you for the question. And yes, they are still a problem. In 2020 alone, over a 6-month period, there were 36 products that were delayed due to late label changes.

*Mr. Carter. When this happens, does the FDA have a -- does the FDA have to review the updated labeling amendment, and that is what significantly delays approval?

*Mr. Gaugh. So the delay goes in a couple of different directions.

First off, the brand company submits their label. The FDA has to review it and approve it. Once they review and approve, then the ANDA that is being reviewed cannot be approved until that ANDA label has been changed to match what the brand company just put in.

Your bill, which we support, will prevent that from happening, giving the FDA the opportunity to go ahead and approve. And then, within 60 days from the approval, the

generic company will make that label change. And of course, you have the one caveat in there: if it is a warning change, then that 60-day period would not happen, the approval could not happen. So that protects the American public.

*Mr. Carter. Good. Thank you, Mr. Gaugh. Thank you for that.

Now I want to talk about my Made in America Act. You know, I have always said there is a difference in recognizing something -- or a difference in recognizing something and realizing it. I think we have all known for some time that we have got too many manufacturers, too many pharmaceutical manufacturers, offshore, and we need to repatriate them and get them back onshore. We realized that whenever this pandemic set in, and whenever we realized just how dependent we were on foreign countries for our pharmaceutical needs and for our PPE needs, as well.

But one thing that this bill also addresses is the advanced manufacturing that we are seeing a lot of now, and that is what the Made in America Act tries to do. It creates an independent pathway that is separate of drug products at FDA to access -- to assess these manufacturing processes.

Dr. Esham, I wanted to ask you, does the FDA currently -- does the FDA's current review process complicate bringing these technologies to market?

*Dr. Esham. I think we -- well, to say that simply, we

have been seeking reforms, and some of that is reflected in the provisions that we advocated for in the PDUFA 7 agreement to require that the FDA -- to get a commitment by the FDA to engage the stakeholders and publish a strategy document outlining specific actions they will take to facilitate the use of advanced manufacturing technologies.

I will also note that we are supportive of the creation of the pathway laid out in your legislation, and will note, generally, that the reason we are -- believe strongly in these kinds of reforms is these technologies offer the ability to optimize efficiency and promote scalable scalability.

*Mr. Carter. Good, good. Thank you. Well, you all are great. We need you on more panels. You all love my legislation, and you are helping me here.

[Laughter.]

*Mr. Carter. I am going to -- Madam Chair, I am going to give you back 19 seconds. Thank you.

Thank all of you all, I appreciate it, and I will yield back.

*Ms. Eshoo. Bravo. Where are you?

*Mr. Carter. Bravo.

*Ms. Eshoo. Are you -- well, feel well soon, okay?

*Mr. Carter. Thank you. Thank you.

*Ms. Eshoo. Wonderful. All right. Dr. Ruiz of

California, you are recognized for five minutes.

*Mr. Ruiz. Thank you for holding this important hearing, and for including my bill, the Diverse Clinical Trials Act.

I am pleased that more and more attention is being paid to equity in health care, and how to address the barriers that are preventing it. As we have discussed in previous hearings in this subcommittee, a lack of diversity in clinical trials is one of those barriers, which is why I introduced the bipartisan Diverse Clinical Trials Act with my fellow doctor and friend, Dr. Bucshon.

This bill seeks to tackle this issue by reducing barriers to participation in clinical trials by allowing researchers to provide necessary equipment to participants, so they can participate remotely or pay for ancillary costs of participation, such as transportation to and from the site of the trial. The bill helps ensure that more patients can participate in trials, regardless of where they live or how much money they make.

As a doctor who grew up in an under-resourced community, practiced medicine in that community, and now represent the largely under-served population, I understand the difference that these flexibilities will make.

I also know the positive effects that increased diversity will have on overall health outcomes. And isn't

the whole point to improve health outcomes for everyone?

It was my mission as a doctor, and it is my mission now, as a Member of Congress.

Dr. Mesa, I hear from companies all the time that they want to create greater diversity in their clinical trials, but they have trouble doing so, even when the will is there. Can you walk us through some of the barriers that researchers face in creating a diverse clinical trial?

*Dr. Mesa. So thank you for the question. And Representative Ruiz, it sounds very much that where you grew up mirrors the challenges that we face in south Texas.

You know, indeed, as we have reflected on these barriers, they are multifold. And I am excited that, you know, many aspects of the bill may help to address them.

You know, one, you know, how do we make it patient-centered? You know, the technologies, the approaches that can make it more feasible to participate, it will evolve. Right now that is evolving as telemedicine. It may be other equipment to facilitate that. It certainly requires some degree of ability to potentially travel for sub-specialized care in a range of ways. And it includes the other parts of, again, really having it be an expectation, as opposed to just a hope.

*Mr. Ruiz. Yes.

*Dr. Mesa. So that, really, the trial is focused --

*Mr. Ruiz. The awareness is also lacking of people knowing that these trials exist, and that they can participate for them (sic). Can you address for us what the real-world repercussions are when you have a homogeneous clinical trial, and how that can affect health outcomes?

*Dr. Mesa. So it can be very clear that, if the trial participants are homogeneous, we really might get the wrong signal in terms of whether a drug is safe or effective. And it may be either more or less safe or effective in any individual group. So that diversity is critical for us to understand how these drugs can be applied to the actual members of our society, not just one sub-group.

*Mr. Ruiz. You know, we -- now let's talk about the non-medical costs. So can you speak to the extent to which non-medical costs, such as transportation and lodging, associated with clinical participation can be barriers to patient enrollment?

And could reducing these barriers also improve diversity?

*Dr. Mesa. These are critical barriers, and trying to overcome them is key. You know, these dollars add up very quickly for transportation, lodging, and other pieces, and can be a complete barrier for individuals that have insufficient resources. So overcoming that is key.

One thing I would like, as I saw in the legislation, is

that they are -- you know, removing them from the category of being inducements. These are not inducements. These are really just allowing feasibility of participation.

*Mr. Ruiz. You know, we have heard a lot about health equity and reducing health disparities. And yet too often track records do not match up to the rhetoric. What can we do to help ensure that companies walk the walk when they are conducting their clinical trials?

*Dr. Mesa. I do think the proposed language that really expects minority accrual plans to really be reflective of the demographics, you know, both of the national population, but also mindful of the disease, as well.

You know, there are certain diseases where we have over-represented groups such as African American men with prostate cancer or others. We need to be certain that there really is sufficient sampling of these groups that are very disease-specific --

*Mr. Ruiz. Or in Hispanics, non-Hispanic steatosis, fatty livers, et cetera. That is predominantly in Hispanics, as well, as well as diabetes.

Look, as a doctor, when we provide clinical care and we look at the evidence, we look at the sample of the individuals that were studied, and there is two big things that we want to look at -- one, randomization; and two, demographics -- to ensure that our prescriptions are going to

work for our patients. And if the sample does not reflect our patient population, then we cannot say with absolute certainty that those -- that study reflects the care for that patient.

Thank you. I yield back.

*Ms. Eshoo. The gentleman yields back. The chair is pleased to recognize the gentlewoman from California, Ms. Barragan, for your five minutes of questions.

*Ms. Barragan. Thank you, Madam Chairwoman, for holding this hearing today to discuss how Congress can help streamline development and approval processes for drugs and therapeutics, strengthening research integrity, and improve diversity and equity in clinical trials.

Speaking of clinical trials, I continue to be concerned with CMS's proposed national non-coverage determination, which severely restricts Medicare beneficiaries' access to an entire class of Alzheimer's drugs. To only provide coverage to only those enrolling in CMS-approved clinical trials means that only a privileged few can participate, further exacerbating health inequities for low-income people and people of color.

There is a staggering amount of work left to do for patients with unmet needs, especially for patients with Alzheimer's disease and other rare and serious diseases. Patients suffering from these diseases are depending on us to

preserve and protect the accelerated approval pathway.

Dr. Allen, my first question is for you. The accelerated approval pathway has been successful in ensuring access to new, safe, and effective drugs for patients most in need of new treatments. This has been particularly true in oncology, where treatments receiving accelerated approval were made available a median of 3.4 years earlier than would have been possible under the traditional FDA approval pathway. Many patients suffering from neurological disorders, like Alzheimer's and Parkinson's disease that lack adequate treatments, are wondering if this level of success can be replicated for their own condition or their loved ones' condition.

My question is, how can the accelerated approval pathway be optimized to help bring promising treatments to patients suffering from neurological disorders and rare diseases, while ensuring their -- they are safe and effective, and what would be the consequences of limiting the accelerated approval?

*Dr. Allen. Thank you very much for the question. You know, I think that, hopefully, the experience in oncology that has been shown about the success of the accelerated approval can be an example of how to extrapolate it to other therapeutic areas.

I briefly mentioned this, but one of the reasons that

this has been so successful in oncology is not necessarily an FDA issue alone. It was one that the cancer research community really came together to pioneer and standardize some of these endpoints, so that they could be well understood, easily applied, and then sufficiently followed up on over time. And I think that is a key reason why we have seen so much success in oncology.

So in thinking about what it would take in order for accelerated approval to be more readily applied to other therapeutic areas like those that you have mentioned, I think it will be a large research infrastructure collaborative endeavor in order to identify and validate those endpoints, in order to make the accelerations that we have seen in oncology available in other therapeutic areas.

*Ms. Barragan. What do you think the consequences are for limiting the use of accelerated approval?

*Dr. Allen. I am sorry, can you repeat that?

*Ms. Barragan. The consequences of limiting the use of accelerated approvals.

*Dr. Allen. If accelerated approvals are inappropriately limited, I think you will see delays in access, certainly.

But I think we also have to be conscious that the hallmark of the accelerated approval process is balancing uncertainties. And so what is made possible by the

validation of surrogate endpoints is a shift in those uncertainties.

I do think the legislations that are being proposed today and being discussed into the future about strengthening that post-market surveillance side of the equation will help reduce those uncertainties over time, and ultimately help expand the development of surrogate endpoints, knowing that there will be a safety net of evidence in place for other therapies, too.

*Ms. Barragan. Thank you.

Dr. Esham, while we have seen significant advances in brain science, therapies for neurological disorders cost more to develop and fail at a greater rate. For example, the Government Accountability Office reported that, in recent years, FDA reviewers denied more requests for and granted fewer breakthrough therapy designations among neuroscience new drug applications, or NDAs, than they did for any other disease area. Could you discuss how a neuroscience center of excellence at the FDA would increase patient access to safe and effective treatments for neurological disorders and conditions?

*Dr. Esham. I think we are still reviewing that legislation, and are happy to have follow-up detailed conversations. But we will -- we concur with your picture about the problems that we are not being as successful as we

want to be in providing clear pathways forward for the development of innovative treatments for neurological diseases. So I am happy to follow up with you.

*Ms. Barragan. Okay, thank you.

Madam Chairwoman, I yield back.

*Ms. Eshoo. The gentlewoman yields back. The chair is pleased to recognize the gentleman from Texas, Mr. Crenshaw, for your five minutes of questions.

*Mr. Crenshaw. Thank you. Thank you, Madam Chair, thank you to the ranking member for having this hearing. Thanks to all the witnesses for being here, as well. And again, thank you, Madam Chair, for -- especially for your interest in stem cell therapy, which I think is a very promising part of regenerative medicine.

*Ms. Eshoo. I am glad to work with you on it.

*Mr. Crenshaw. Thank you. And as you know, I introduced a bill recently with Dr. Burgess that would require some updates to a 20-year-old regulation at FDA, specifically looking at the definition of "minimally manipulated,'' as -- especially as it relates to adipose stem cells. And I know we are not able to consider it at this legislative hearing, but I absolutely appreciate the chair's willingness to work with me and my office on including it in the final bill.

The FDA has been able to do a lot for innovative

medicine, but hasn't been able to move forward with novel approaches to regenerative medicine -- not just curing diseases, but renewing and replacing parts of the body that are diseased or no longer working.

Many of our regenerative medicine projects are working on ways to renew and replace cardiac, liver, lung, muscle, and even ocular tissue. To oversee these treatments, the FDA has relied upon a regulation that was written in 1997 and finalized in 2001, which is, of course, what we are looking at asking the FDA to possibly reform.

Dr. Mesa, this is for you, because it is my understanding that one of the treatments for leukemia, which you specialize in, can be autologous or allogeneic stem cell transplants derived from bone marrow. And so I am wondering if you have input and -- you know, onto these potential reforms to this 20-year regulation, and maybe what safeguards we should be mindful of as the FDA looks at that.

*Dr. Mesa. You know, without question, the ability to use cellular therapy has had an enormous impact on cancer. You know, continuing to modernize the regulation to expand that is well worthwhile.

You know, autologous and allogeneic transplant have had a huge impact on bone marrow disorders. And we continue to evolve now to cellular-based therapies, you know, that are leveraging the immune system in a range of ways. So I am

certainly strongly supportive of that evolution to allow these technologies to continue to evolve, to really expand how therapies can impact cancer and other diseases.

*Mr. Crenshaw. Okay, thank you. And what was the FDA worried about in stem cell therapies in 2001 that maybe they don't need to be worried about today?

How has the science changed to allow more access to regenerative medicine?

*Dr. Mesa. I think the ability to really, you know, utilize, you know, more differentiated cells, or take more differentiated cells, indeed, differentiate them to utilize them, you know, there -- certainly, there was always the concern in terms of, you know, in -- derived cells, in terms of the initial piece. But now, with the ability to really leverage cells further on, it really is pushing regenerative medicine in, you know, many exciting directions.

*Mr. Crenshaw. Thank you.

For Dr. Vereshchagina, the same office working on regenerative medicine is also responsible for gene therapy and CRISPR technology. What should the FDA be doing to expedite the chemistry, the manufacturing, and control of the CMC review process, so that advances in regenerative medicine and gene therapy vector manufacturing can move forward more quickly?

*Dr. Vereshchagina. Thank you for the question.

Manufacturing issues, especially for cell and gene therapies, are very top of mind and ripe for discussions. And this is why industry discussed these issues with FDA. And we inserted specific provisions in PDUFA 7 agreements that would make sure that FDA pays attention to those issues, that there are stakeholder discussions, that innovative manufacturing technologies are considered for these, specifically for these therapies, to make sure that manufacturing does not become a roadblock, essentially, for the development and timely approval of cell and gene therapies.

*Mr. Crenshaw. Thank you, and I yield back.

*Ms. Eshoo. The gentleman yields back. It is a pleasure to recognize the gentlewoman from Delaware, Ms. Blunt Rochester, for your five minutes.

*Ms. Blunt Rochester. Thank you so much, Madam Chairwoman, for the recognition, and thank you to the witnesses for being here for this important and timely hearing on the future of medicine.

I am pleased we are considering legislation that will accelerate the discovery, development, delivery, and accessibility of medical treatments and cures. I also appreciate the opportunity to highlight issues that are important to Delawareans and many others across the country.

Increasing diversity in clinical trials is a shared goal among the members of this subcommittee. In late 2020 the FDA

released recommendations on approaches that sponsors of clinical trials could take to increase enrollment in under-represented populations in their clinical trials. The guidance includes recommendations like broadening eligibility criteria in later stages of development, reducing the frequency of study visits, using mobile medical professionals, and making participants aware of financial reimbursements for expenses associated with participation.

Trial sponsors of almost every disease struggle with enrolling inclusive populations, and Alzheimer's disease is no exception. My bipartisan Equity in Neuroscience and Alzheimer's Clinical Trials, otherwise known as the ENACT Act, builds on these FDA recommendations, and strengthens the capacity of the NIH to increase the participation of under-represented populations in Alzheimer's clinical trials.

Specifically, the bill expands education and outreach to these populations, [inaudible] diversity of clinical trial staff, encourages the use of innovative trial designs, and reduces participation burden.

Dr. Vereshchagina, do you believe that the recommendations in the 2020 FDA guidance on enhancing the diversity of clinical trial populations are achievable?

And what barriers are there for trial sponsors interested in fully adopting [inaudible]?

*Dr. Vereshchagina. Thank you for the question. So

while we don't have a position on this specific bill, we agree that new treatments are desperately needed for Alzheimer's. And biopharmaceutical companies are committed to research and development in this area.

*Ms. Blunt Rochester. Do you believe there are any -- are there any barriers for trial sponsors that you know of?

*Dr. Vereshchagina. So, you know, in general, there are known barriers for clinical trials. Many of them were mentioned today, such as awareness of clinical trials; access for patients to clinical trials who may not be able to travel to big, established centers; lack of community-based clinical trial sites; lack of diverse health care providers that can serve as ambassadors to make sure that there is a diverse population participation in clinical trials.

*Ms. Blunt Rochester. Great. Thank you.

And Dr. Mesa, you wrote at length about the importance of empowering community providers to communicate openly with trial-skeptical patients. You note that evidence suggests that trial-skeptical patients in under-represented groups are willing to consider participating in clinical trials if they can discuss all of their concerns with a provider they trust. And for that reason, my bill, the ENACT Act, would facilitate the connection between researchers and clinicians with deep ties to the community with cutting-edge Alzheimer's disease research centers.

How will building bridges between study investigators and community providers potentially increase the participation of under-represented populations in clinical trials?

*Dr. Mesa. Well, clearly, it takes teamwork to take great care of patients, whether it be Alzheimer's or cancer. You know, community providers, as well as other community partners, whether it be churches, you know, other organizations and groups, you know, and the treating physicians and the clinical trial physicians is really critical, you know, to demystify the process, to build trust.

To be able to understand all of the treatment options -- clinical trials are just one option, so patients really have to understand the full scope. In south Texas we found that having the family health expert present at the discussion of all options, including trials, has been very impactful to try to increase satisfaction with the process, as well as enrollment.

*Ms. Blunt Rochester. Great. Thank you so much.

Lastly, I want to thank all of the stakeholders and the families -- many of us have been personally touched by Alzheimer's -- as well as Representatives Herrera Beutler, Smith, Waters, and my E&C colleague, Representative Curtis, for working so diligently on this bill.

And I am also looking forward to passing the FDA

[inaudible] bills on time, so that the FDA can fulfill its mission of protecting the public health.

Thank you, Madam Chair, and I yield back.

*Ms. Eshoo. I thank the gentlewoman. It is a pleasure to recognize another one of the outstanding doctors on our subcommittee, the gentleman from Indiana, Dr. Bucshon.

*Mr. Bucshon. Well, thank you, Madam Chairwoman, and thanks for this hearing. Thank you to all the witnesses. This will be some ground we have already covered, as it relates to diversity in clinical trials. But this tells you how important this is to this subcommittee.

Many, many people on both sides of the aisle support advancing clinical trial diversity legislation out of this subcommittee. As a doctor, I know the importance of needing diverse participation in trials to better understand how the drug treatment and/or vaccine will respond to different patients I would see in my practice, just as I know from my medical training that certain diseases may affect certain patients differently based on a multitude of factors, including genetics and ethnicity.

As the future of medicine continues to move towards personalized medicine, this will only continue to become more and more important. That is why I partnered with my good friend, Dr. Ruiz, to introduce H.R. 5030. This bill would help promote clinical trials having proportionate

representation of all communities, as well as support education, outreach, and recruitment for future clinical trials.

Currently, as we have discussed, there is a number of external factors that make representative enrollment challenging: for example, patient and provider awareness, access to trial sites, and sometimes patient out-of-pocket costs. One way to help address those barriers, which is included in H.R. 5030, is to allow for more flexibility for sponsors to provide additional support to individuals from historically under-represented groups without running afoul of the anti-kickback statute or civil monetary penalties.

Dr. Esham -- is that how you pronounce your name, Esham?

Could you discuss how these interventions could or would make trials more representative of the population?

*Dr. Esham. Thank you for the question, and I will -- I think we are continuing to work with your office on this bill, and --

*Mr. Bucshon. Yes.

*Dr. Esham. -- look forward to having those continued discussions.

We certainly, as in my written testimony stated, we certainly see the value and the potential of decentralized approaches, the utilization of digital health tools to help us sort of break down some of the existing barriers that may

have led to less diverse trials in the past.

In terms of some of the other provisions, I think we just want to work with you to make sure that -- and again, I have already said on the record --

*Mr. Bucshon. Yes.

*Dr. Esham. -- trial safe harbors have been very effective. But we do want to work to make sure that any other kinds of discussions relating to those types of things do come with adequate protections for patients. So we just want to continue to work with your office.

*Mr. Bucshon. Understood.

*Dr. Esham. I would also like to just note for the record -- a little bit of sell here, on my end -- we do have some proposals that we have developed, as well, that we think would add additional activities, and lead to specific guidances on issues, on additional issues that we think need to be resolved to continue to advance a more inclusive paradigm.

*Mr. Bucshon. Great. And Dr. Mesa, you touched on it in your testimony, but could you further expand and elaborate on why decentralized trials are so important to the promotion -- and more diverse participation in clinical trials?

And I know we have covered some of this ground, but this is how important this is. We really need to continue this discussion.

*Dr. Mesa. So it really is critical. I think, first, you know, aspects -- as well of the bill that you have introduced -- that really helped to facilitate the community partners that can really play a piece in that, it really is, I think, a network, where you have really community providers potentially playing a piece, you know, and what that looks like, the -- obviously, all the telehealth solutions, and some of that really can even begin with, really, the initial screening for a trial. You know, is it an option? You know, is it worthwhile for the patient to travel to whatever center for their enrollment?

You know, and then finally, you know, as it relates to the critical planning piece, you know, as the trial is developed, you know, how are these kind of telehealth solutions built in to make the trial the most feasible for participation?

*Mr. Bucshon. Yes. So you think some of the policies in 5030 could encourage a more diverse participation in clinical trials?

*Dr. Mesa. I think it could be very impactful. I think there are several key aspects from telemedicine, the transportation, and other that I think really could be genuinely impactful, as I think about both the south Texas issues of diversity, but also, really, the rural and distant barriers.

*Mr. Bucshon. Yes, I just want to say in finishing that, you know, we have seen this play out over the last couple of years with vaccine reluctance in certain groups of our fellow citizens, because I think a big piece -- and I think a big piece of that was the lack of diversity in the clinical trials related to the vaccines. And, you know, people understand this, and that is why we need to do better. This played out in real time with vaccine reluctance in certain populations, whether it is in rural America that I represent, or other areas of the country.

So thank you all for being here, and I yield back, Madam Chairwoman.

*Ms. Eshoo. The gentleman yields back. It is a pleasure to recognize the gentlewoman from New Hampshire, Ms. Kuster, for your five minutes of questions.

*Ms. Kuster. Thank you so much, Madam Chair, and thank you for hosting this -- chairing this important hearing.

I hear consistently from Granite Staters about how their prescriptions are simply too expensive. I myself picked up a prescription last month, and they charged $182. And this is a monthly asthma medication. So I was looking at how my constituents are having to make impossible decisions about paying for other necessities like rent or mortgage, or food for their children, while still taking their medications.

I think we can all agree medication is only as good as

it is affordable and accessible, and that is why I recently introduced the Increasing Transparency in Generic Drug Applications Act that would ensure that the Food and Drug Administration can adequately provide feedback on proposed drug formulations to generic drug applicants to speed up the process, make it more streamlined, and make more generics available to consumers. This would address a major barrier to generic drug approval, and expedite patient access to affordable medication.

Mr. Gaugh, could you explain why this bill is important to patients, and how this information will expedite development and access to complex generic drugs?

*Mr. Gaugh. Thank you for the question. Yes, you are referring to what we refer to as Q1, Q2, which is qualitative and quantitative review.

And what we have found, since 2017 -- pre-2017, when we would submit a drug, we know what the active ingredient is, we do not know what the inactive ingredient is, or the concentration of an active ingredient. So when we would submit a drug prior to 2017, as we went back and forth to the FDA, the FDA would reveal what that product is, and not necessarily what the concentration is, but would give us a range to go up and down.

Since 2017, the FDA has changed that premise. And now, when we submit an application and we are going through that

review of trying to determine what the inactive ingredient and the concentration is, we have to go through a controlled correspondence process. And the FDA has limited that process to three products in the correspondence. There are probably more like 12 to 15 products that could be considered. We do three. We either get accepted or rejected -- many times rejected. Then you do another one with three more. So it takes a significant amount of time to move that forward.

*Ms. Kuster. It sounds like --

*Mr. Gaugh. In gaining approval.

*Ms. Kuster. -- a painful guessing game. In fact, this issue was identified by the FDA in 2021 in a report entitled, "HHS Comprehensive Plan for Addressing High Drug Prices as an Obstacle to Patient Access to Lower Cost Drugs.'' My bill would clarify that the FDA can provide generic drug applicants with improved directional guidance on their proposed formulation for complex generic drugs. This information is critical for the development and timely approval of affordable medicine for patients.

How important is this information for generic drug developers, and do you think this legislation will result in expanded patient access to affordable medication?

*Mr. Gaugh. So this is critically important to our industry, and we support your legislation that you put forward because, as you said earlier, and I said in my

previous statement, the time that it takes to go in this back-and-forth game can be a significant period of time, and delays access to the American public by many, many months, if not more into years.

*Ms. Kuster. Thank you.

Well, with that, Madam Chair, I hope you are pleased. I yield back with a minute left to go.

*Ms. Eshoo. Wow, you win the lottery. You win the lottery. Very generous. We thank the gentlewoman for all of her good work at our subcommittee.

Now it is a pleasure to recognize another member that is respected here, another one of our doctors, Dr. Joyce from Pennsylvania.

You have five minutes for your questions, sir.

*Mr. Joyce. Thank you for yielding, Madam Chair Eshoo, and thank you, Ranking Member Guthrie, for holding this hearing today. And thank you to our distinguished panel for being present on this rainy St Patrick's Day.

As I have said before, the safe, consistent, and prompt approval of new pharmaceuticals, biologics, generics, and biosimilars are critical to the health of our constituents. As we look towards the next iteration of user fee agreements at the FDA, it is also very important that we work to ensure continued access of medication for all patients.

I would like to thank my colleagues, Representative

Matsui, Representative Griffith, and Representative Barragan for working with me on legislation to fix the REMS programs that would give the FDA authority to provide more transparency and accountability in the REMS programs, and to end the current disruptions that we have seen to both isotretinoin and clozapine REMS. This will ensure better continuum of care, and access to medications, and ensure patients and health providers the feedback that is heard on changes to this program before they go into effect.

I would also like to thank Congressman Levin for working with me to introduce bipartisan Drug Manufacturing Innovation Act, which we are considering here today. This important legislation will codify the FDA's emerging technology program, which will encourage better communication between the FDA and industry to identify and resolve technical and regulatory issues with novel technologies prior to the submission of an application with the FDA. This approach of working with industry will foster more innovation, and get new cures and breakthrough therapies to the patients faster.

My first question is for you, Dr. Esham. Can you please discuss why there is sometimes slow adoption of novel technologies to manufacture drugs?

And the second part, do you believe regulatory uncertainty by the FDA plays a role?

*Dr. Esham. So I -- hopefully, I am answering your

question, but I just wanted to point out that we are supportive of your bill. We strongly support the emerging technology programs mission, and want to continue to -- I believe it will have great, great benefit, including with the guidance and the funding.

And I may need you to repeat the question one more time.

*Mr. Joyce. Do you think that, by having regulatory uncertainty in the FDA, that that plays a significant role in allowing manufacturers to get these great new novel medicines that patients need?

*Dr. Esham. I think we are always working with the FDA to try to get regulatory clarity across the board. And again, the more novel a medicine is, where the less precedent is, the more you have to really engage with the FDA on a very active basis. And we at BIO really try to work with our members to do that on a very timely basis to avoid undue delays.

*Mr. Joyce. And do you think that access to innovation really should be one of the components of American access to medicine, American ingenuity, and American health care?

*Dr. Esham. Yes. I mean, I -- you know, I think we should all -- you know, when we reflect upon what we have done in terms of transforming medicines to date, it is really just -- we should always be thinking about that as the first step, and really try to keep working towards the next vision

of really transforming how we can provide better care for patients.

*Mr. Joyce. I think you nailed it with that comment, that that is an obligation both here, as Members of Congress, and as industry to provide better medication for our patients.

Finally, I want -- do want to flag some concerns that I have with proposed changes to the accelerated approval pathway. Dr. Vereshchagina, would it be accurate to say that since only medicines for serious conditions that address an unmet medical need are eligible for this pathway, that the accelerated approval offers significant benefits to patients by making important medicines available much earlier than would have otherwise been the case?

*Dr. Vereshchagina. Absolutely, and thank you for this question. I think it is always important to remember the original intent of this bill, that -- exactly what you said, it is to provide access to medicines for patients with serious and life-threatening conditions who otherwise don't have options.

And it is critical that the -- what the accelerated approval pathway does, in its current form, to providing that ability for industry to continue to invest in research and development for those unmet medical needs, and have that regulatory predictability to deliver safe and effective

medicines for patients who otherwise would not have those medicines.

*Mr. Joyce. Thank you. I see my time has expired.

Thank you, Madam Chair, again for convening this important hearing today. I yield.

*Ms. Eshoo. Thank you. The gentleman yields back.

The chair now recognizes the gentlewoman from Washington State, another outstanding doctor on our subcommittee, Dr. Schrier.

You have five minutes for your questions.

*Ms. Schrier. Well, thank you, Madam Chair, and thank you to the witnesses for coming today and sharing your knowledge. And thank you to all of my colleagues for putting forward these important pieces of legislation.

I am particularly happy to see Representatives DeGette and Upton's bill, Cures 2.0, on the docket for today. Dr. Bucshon and I have a provision in this bill, the Meaningful Access to Federal Health Plan Claims Data Act -- there is a mouthful -- which allows clinical researchers to have access to Medicare claim data.

So this means that physician researchers can see trends in patient diagnoses and treatments, giving them data that can help both with research and with providing better care for their patients. And it is well known, for example, that some medications work better for some patients. And often we

figure this out by trial and error, but later find out that there is actually certain sub-categories of patients that make them more or less likely to respond to a given medication. And without big data from CMS, from Medicare, it can take a long time to figure that out. So access to those vast quantities of data can help define which patients will do best with which medications, for example. And that is good for patients, for timing and for pocketbooks.

Now, there is another example, which I thought was interesting. Like, some cardiothoracic surgery patients do worse after a blood transfusion. And with only a handful of cases, a surgeon might just assume that these were random, bad luck. But having access to massive troves of Medicare data allowed clinical researchers in Virginia to find patterns, and discern which specific characteristics and medical histories of those patients made them more likely to worsen. And that means doctors can give better care and be highly vigilant for adverse outcomes if those patients need blood transfusions.

Dr. Ramachandran, in your testimony you point out [inaudible] transparency in post-market approvals, clinical trials, and more. And as a practicing physician, can you just briefly talk about how having access to Medicare claims data and more data just helps you do research to treat your patients at Yale?

*Dr. Ramachandran. Yes, definitely. Thank you, Congressman, for the question.

The -- you know, that provision is so important, especially as a physician researcher, but someone who takes care of patients. You know, we have talked today about the limitations of clinical trials in terms of sometimes not enrolling patients from certain populations who have certain disease conditions, and so that makes it so critically important to have robust post-marketing surveillance and, really, access to data such as claims data, so that we actually know whether or not the drug actually works in the patient that we are seeing in the hospital or the exam room.

And so for me, as a practicing physician, I really want to know whatever drug or device I am going to be prescribing or recommending to a patient actually works with them, works for them. And that sort of claims data is just so critical, not just to inform my own practice, but also the guidelines of rapidly, you know, changing medical practice, so that we can be able to do better medicine for our patients.

*Ms. Schrier. Thank you. It is almost like a macro level of precision medicine.

I wanted to turn my attention -- because transparency is a theme today, I want to pivot to drug -- to medications. Mr. Gaugh, I was flabbergasted when I read your testimony detailing the process that generic drug manufacturers have to

go through to get to the market.

I think we all know that they have to match up exactly in quantity and quality with the active ingredient. But you talked about having to exactly match the inactive ingredients, the fillers, the things that really don't impact efficacy, and that they can't just get that information from the brand name manufacturer, they have to go in and guess, and sort of trial-and-error this, which can really delay the arrival of these generics to market. That is incredibly frustrating, as a patient, but also as a legislator and a doctor, to know that this kind of guessing game is keeping less expensive medications from our patients.

Can you point out some of the commitments in GDUFA 3 and the BsUFA 3 that will help increase transparency and, ultimately, facilitate this speeding of generics to market -- and biosimilars?

*Mr. Gaugh. Thank you for the question. We did have these discussions during GDUFA 3. But unfortunately, no resolution came out of that. So I am very happy to see this bill come forward around Q1, Q2, and being able to get the information.

In an earlier statement I noted that the FDA, prior to 2017, did provide that information without what we call a back-and-forth guessing game of what that product is. So we would submit a -- now, today -- we submit a controlled

correspondence with just three products in it, three inactive ingredients. The FDA would then come back and say either, yes, that is acceptable, or no, it is not. If it is not, then we go back with three more ingredients, and three more, until we do get an acceptable.

So this changed in 2017, as I said a few minutes ago, and so we are looking forward to a bill like this that would move that back to giving that information. Because, prior to 2017, they would tell us what that inactive ingredient was.

Concentration, we still had to kind of go with thumbs up, thumbs down, whether we were headed in the right direction. But it was a much, much quicker and much less guessing game. Thank you.

*Ms. Schrier. Thank you. My team will stay in touch with you about that provision, and I yield back.

*Mr. Gaugh. Wonderful.

*Ms. Eshoo. The gentlewoman yields back. Let's see, the gentlewoman from -- you are good on your side? Okay. Hold on, witnesses. This is going to end.

*Mr. Guthrie. No, we don't have anybody.

*Ms. Eshoo. This is going to end pretty soon. For your patience, we all thank you.

The gentlewoman from Massachusetts, Mrs. Trahan, you have -- recognized for five minutes.

*Mrs. Trahan. Well, thank you, Chairwoman Eshoo. Thank

you, Ranking Member Guthrie, for convening this hearing. Thank you to the witnesses for your patience and your expertise.

Over the past two years we have seen how streamlined development and approval processes, specifically for COVID-19 vaccines and therapeutics, have been critical to saving lives. And I am thrilled that this committee is considering the 22 bills before us today to broaden that focus to encompass additional diseases that currently lack robust biomedical research and innovative treatments.

Patients from under-representative populations are disparately impacted throughout our medical system, from cancer treatments to drug development to sepsis detection algorithms. And the need for diversity in clinical trials, which we have been discussing today, mirrors a similar need for diversity in data sets used to train medical software, an issue my office has been working on.

So, Dr. Mesa, my first question is for you. When a clinical trial's results are not statistically significant for a given sub-population, how are those limitations communicated to physicians?

*Dr. Mesa. So certainly several mechanisms, both in terms of, you know, as a result, is published in a manuscript.

But really, the greater discussion that occurs, you

know, at national meetings, you know, and subsequent activities -- you know, it is critical -- there are times we just don't have the power to detect a difference, but we suspect that a difference may be there, and requires additional trials to be performed, additional sub-analysis to be performed, or for us to be able to try to tap into, you know, other experiences after a drug is developed, in terms of real-world evidence.

So it is a challenge. I think that is a challenge we all feel in terms of -- you know, sometimes we just don't have enough power in a study to be able to answer all the questions that are relevant.

*Mrs. Trahan. Sure. And as a medical practitioner, what do you think about as you work with patients from groups traditionally under-represented in clinical trials?

I mean, do you yourself take extra steps when you notice unusual reactions to drugs or treatments?

*Dr. Mesa. Most definitely. You know, it is really a critical piece.

Colleagues in Ecuador identified an unusual reaction to a medicine we frequently use here, in the United States, rituximab. That was related to, you know, indigenous cuisine of -- the medicine is developed out of Chinese hamster ovary cells. And these individuals that have had guinea pigs as part of their diet, you know, had unusual reactions.

So again, just a bit of an extreme example, but again, different cultural pieces, whether it be related to genetics, culture, or diet, sometimes might have some really unexpected consequences. And then we try to communicate these to really be sensitive to those differences.

*Mrs. Trahan. Got it. Thank you for that.

Dr. Esham, when crafting and designing a trial, do trial sponsors take steps to determine whether a trial is significantly diverse? And if so, how do they do that?

*Dr. Esham. I mean, they often do do that. I think what we have heard from our member companies, and where we want to drive activities that can lead to regulatory alignment about approaches for all clinical development programs -- and that is we need to address some gaps in our data -- in our reliable data sources.

We need to come up with some methodologies and a line of methodologies about how we can use the data that is available, why we are continuing to improve the data that will help us establish targets that are representative of the patient population. So we have heard that as a sort of inconsistent barrier that we want to resolve.

So that is just one example of some of the proposals that we have brought forward to this committee.

*Mrs. Trahan. Thank you for that. Well, I certainly look forward to passing legislation aimed at ensuring

thorough testing and research, that medical treatments are safe and effective for all members of our society, and I appreciate the time.

I appreciate this hearing, again, and these 22 bills being brought forward, Madam Chair. With that, I will yield back.

*Ms. Eshoo. The gentlelady yields back. The gentleman from California, Mr. Cardenas, good to see you, and you have five minutes.

*Mr. Cardenas. Thank you so much, Madam Chairwoman, and also thank you to Ranking Member Guthrie.

This hearing is incredibly enlightening, and I want to thank all the incredible witnesses for all of your professional testimony and giving us some information about what is going on today, and what we need to do better in our country.

I apologize, I had to step away from the committee just for a little bit, as 988, when it comes to mental health, is going to be live in July of this year, which is a great thing, and we need to make sure that we do our part in Congress to support it.

I want to spend time today talking about the importance of vetting therapies and clinical trials that mirror demographics nationwide. There is no question that this is desperately needed to ensure the safety and efficacy of drugs

for everyone, especially in an increasingly diversifying country with pronounced health inequities from community to community.

Clinical trial diversity is something we hear is a priority across the board, thank God, but not just on principle, but as something that benefits every actor in the process: from industry, who wants to produce a high quality, effective product, from the agencies that want to protect patients, and from consumers who want assurances that their medications will work for them just as intended. Despite the consensus, we hear concerns about hesitancy and inability to recruit patients of color to participate in clinical trials.

Dr. Mesa, you have clearly had some success in recruitment efforts at the Mays Cancer Center. I am thrilled to hear that you were able to boost enrollment of Hispanics from 46 percent to 56 percent after instituting demographic-specific plans. Can you give us an example of how you were able to do that, and maybe something that could be enlisted as a best practice in other trials?

*Dr. Mesa. So it is a mandatory part of our protocol review process now that the investigators and the entire team really reflect on each trial individually. All of these trials are quite heterogeneous. And as we reflect on the eligibility criteria, as we reflect on the conduct of the study, the ability to have transportation support or others

-- we have provided transportation support through philanthropic funding, you know, as one mechanism to help to support individuals.

What we found is every trial is different, and really trying to have a plan per trial is really critical.

I think the other piece of this, without question, is increased feedback that we are having with our colleagues in the pharmaceutical industry, really, regarding the actual design of the study, the eligibility criteria, but also the rigorousness of the number of visits, the utilization of telehealth all can have a real impact on best practices.

*Mr. Cardenas. Well, thank you. And with that, your response highlights the need for clear and enforceable benchmarks as such. I am proud to be a co-lead on a bill which has to do with Clinical Trial Diversity Act of 2021, which would help institute these types of requirements for NIH-funded trials.

I believe the Clinical Trial Diversity Act is a necessary step to ensuring that our therapies work for everyone. And I am grateful for my colleague, Representative Robin Kelly, who has been a true leader on this legislation and other pieces of legislation like it.

Finally, just to pivot briefly, I would also like to state that I am pleased to see that legislation to move away from animal testing is being considered, especially as more

human-centered alternatives continue to emerge and become more of a standard. I am supportive of many bills that attempt to make this transition, and I believe we need to consider a host of measures to achieve this goal. Focusing on more humane approaches when possible is beneficial for both animals and humans.

Dr. Mesa, I would also like to ask you if you have had success on recruiting not only at the college level, or earlier in people's decisions to get into health care.

*Dr. Mesa. I hope that we have made a difference by trying to really engage people earlier and earlier in their career --

*Mr. Cardenas. Have you been able to engage people at younger ages? Middle school, high school?

*Dr. Mesa. So we have gone down to the high school level, but certainly it is under consideration, you know. How do we make careers in health care and STEM, you know, attractive for, you know, the people in our community? We live in a minority-majority community in San Antonio, in south Texas. And it is a key part. You know, giving opportunities, internships, opportunities to really grow and succeed along a variety of paths.

*Mr. Cardenas. Thank you. I have been to south Texas, a lot of hard-working, beautiful families, mostly Latino families. And I would love to see them use their talents and

abilities in this field.

With that, my time has expired. I yield back. Thank you so much, Madam Chairwoman.

*Ms. Eshoo. The gentleman yields back, and now the ever-patient, ever-present Congresswoman Diana DeGette, who is the lead author, together with Mr. Upton, on Cures 2.0.

So thank you, Diana --

*Ms. DeGette. Thank you so much.

*Ms. Eshoo. -- you are recognized for five minutes.

*Ms. DeGette. Madam Chair, thank you so much. Thank you for your leadership. For somebody who is kind of a medical research wonk, I don't like anything more than sitting here listening to these 22 bills being discussed. And I want to thank you for your partnership with me and Chairman -- or Congressman Upton on both ARPA-H and Cures 2.0. These bills will move together, and they will be revolutionary.

So, you know, when Fred and I teamed up in 2015, we really did envision a transformative bill that would accelerate the discovery, development, and delivery of medical treatments and cures. And when I hear about all these bills today, and I think about the things we did in that bill that started the movement, I am so thrilled to see these bills moving it ahead.

For example, my friend, Congressman Cardenas, was

talking about the Clinical Trial Diversity Act, which is such an important key. And in 21st Century Cures we started that movement towards diversity in clinical trials, and many, many other issues.

And so I want to ask you, Dr. Esham, how have the policies that were included in 21st Century Cures, like NIH's regenerative medicine innovation project, FDA's real-world evidence program, and patient-focused drug development impacted the progression of biomedical innovation?

*Dr. Esham. The simple answer is very positively. And it really has led to -- I think it built a lot of foundations for continued innovation in how we approach drug development, how we enable the development of novel treatments. So again, it has been very important and very beneficial.

*Ms. DeGette. And do you think there is more that we can do to improve existing research and regulatory pathways to help the progress of medical innovation?

*Dr. Esham. Well, I have been working with biotechnology companies for the better part of 12 years, and I think we are always of the mindset we can always do better, we all -- we must always improve. And there is always a new vision to be met. So there is always more work to be done.

*Ms. DeGette. And have you looked at Cures 2.0?

*Dr. Esham. Yes, and I can --

*Ms. DeGette. And what is your organization's view of

that bill?

*Dr. Esham. Yes, and I can quickly -- I will try to be succinct.

We are very supportive of the provision relating to the advancement of digital technologies and real-world evidence.

We are supportive of the provisions relating to increasing clinical trial diversity.

And again, we have some additional ideas we would love to talk with you about.

And we were very supportive of the provision that reinforces the importance of PASTEUR. And as I stated earlier in my testimony, you know, we must recognize that antimicrobial resistance is a leading cause of death, and it does have unique challenges to getting incentive and driving development of those medicines. So we really urge Congress to pass PASTEUR this year.

*Ms. DeGette. Thank you. Dr. Allen, how have previous Cures policies benefited patients and their loved ones?

*Dr. Allen. Well, thank you very much for your leadership on both initiatives. I think what was very quickly seen from the Cures 1.0 initiative, what really stands out, were the provisions to operationalize aspects related to patient experience and patient-focused drug development.

And I think before Cures 1, there was at least initial

attempts to think about ways to engage patients more frequently. But through the operational steps around methodology and processes that were laid out in the first Cures provisions, it really enabled those to move forward. And we have seen that, in terms of an understanding and more available information for patients.

*Ms. DeGette. And have you looked at Cures 2.0, Dr. Allen?

*Dr. Allen. We have.

*Ms. DeGette. And do you think that Cures 2.0 helps further that even more?

*Dr. Allen. Absolutely. I think there is important provisions in 2.0 that recognized the advancement of technology specific around things related to cell and gene therapies, including aspects around looking at additional systematic enhancements such as the improved communication between CMS and FDA to ensure that there is a timely handoff between these new breakthroughs that are being enabled through a strong research system to make it all the way accessible for patients.

*Ms. DeGette. Great. Thank you. And have you looked at Cures 2.0? Does Friends of Cancer Research support that legislation?

*Dr. Allen. We absolutely support it, and I look forward to working with you as you move forward through the

process.

*Ms. DeGette. Great, thanks.

Thank you so much, Madam Chair. I yield back.

*Ms. Eshoo. The gentlewoman yields back. And it is a pleasure to recognize the gentleman from New York, who is -- are you waiving on? Yes.

Just so that the witnesses know, members of the full committee who are not members of our subcommittee choose to waive on, and we always welcome from both sides of the aisle when they do so.

Congresswoman DeGette has waived on today, and now, Mr. Tonko, you are waiving on, and you have five minutes.

*Mr. Tonko. Thank you, Madam Chair, for allowing me to waive on and, more importantly, for your leadership of the Subcommittee on Health.

And again, thanks to Chair Eshoo, and Ranking Member Guthrie, and Chair Pallone, and Ranking Member McMorris Rodgers for including the Helping Experts Accelerate Rare Treatments Act of 2022, or the HEART Act, on today's agenda.

I wanted to take a moment and thank Chair Pallone and his staff for their energy and dedication to working with my office to develop this HEART Act fully.

Three years ago I had the pleasure of meeting a constituent, Melissa Goetz, who is the co-president of the Familial Chylomicronemia Syndrome, or FCS, Foundation. FCS

is a rare genetic condition that causes a buildup of fats in the blood that can increase the risk of severe abdominal pain and potentially fatal attacks of pancreatitis. FCS presents a significant risk of severe and life-threatening attacks of pancreatitis and early death, even amongst patients who are in treatment to manage the condition. Melissa's daughter, Giuliana, was diagnosed with FCS when she was three weeks old. She was hospitalized with pancreatitis, a liver infection, and kidney infection at seven weeks old. Well, I am pleased to share that Giuliana is doing well today.

It came to my attention that potential treatment for this condition was ultimately rejected, in part because it would require a weekly blood draw that the Food and Drug Administration deemed to -- as too burdensome to patients. This prompted me to consider how FDA is currently engaging with patients, especially those that suffer from rare and ultra-rare diseases that do not have treatment options today.

I drafted the HEART Act with my friend and colleague, Congressman McKinley, to ensure that FDA is appropriately engaging with medical experts and patients during its review process.

The HEART bill requires an annual report to Congress to better understand how FDA processes submissions for treatments for rare diseases, and how it engages with external experts such as patients and physicians.

It also requires a study to do better -- to better understand how the EU manages its rare disease treatment reviews.

It has the Government Accountability Office assess how the FDA is engaging patients and experts in the review process, and provide recommendations to improve these interactions in the future.

It also requires the FDA to hold a public meeting to solicit feedback from patients, patient groups, and medical experts on how it could better incorporate its expertise during a review of a treatment.

Dr. Allen, the HEART Act is designed to better incorporate both the patient and rare disease or small population studies medical experts' perspective during the FDA review process. Do you agree that, especially as it relates to rare and ultra-rare conditions, that we can do more to better incorporate the patient and rare disease medical experts in that FDA process?

*Dr. Allen. Definitely. I think we have seen that across other therapeutic areas, where enhanced communication very early on with FDA has been beneficial in designing the studies appropriately to get new medicines forward, but also helping them in their regulatory review, ultimately.

*Mr. Tonko. Thank you.

And Dr. Mesa and Dr. Esham, can we do more to better

incorporate the patient and rare disease expert perspective into the FDA process?

*Dr. Esham. I concur with my colleague, Jeff. I mean, there is always benefit to ensuring more engagement with more experts, particularly in diseases that -- where little precedent is set, or just newly diagnosed.

And I would also like to say I am glad to hear, in the story that you told, that the individual is doing better.

*Mr. Tonko. Yes. Thank you, Doctor.

And Dr. Mesa?

*Dr. Mesa. Yes, most certainly. I did participate -- I focus on rare chronic leukemias, and was involved with kind of an FDA listening session -- again, really led by patients, where they brought in patient voices, really, from across the spectrum of disease to both counsel on clinical trials, that process, as well as, you know, what were clinically meaningful endpoints. So I think that is an important piece for rare diseases.

*Mr. Tonko. Thank you. And I also would like to note my strong support for the Prevent Interruptions in Physical Therapy Act, which is about locum tenens, the ability to bring in a replacement provider during a provider's temporary absences for illness, pregnancy, vacation, or continuing medical education. The 21st Century Cures Act contained a provision that added physical therapists to the health care

professionals that may use locum tenens under Medicare, but was limited for rural and under-served regions. The Prevent Interruptions in Physical Therapy Act would expand this for all geographic regions.

So I look forward to working with the sponsors of Cures 2.0 to get this included as the legislation moves through the process, as we did back when it was included in Cures 1.0. This will indeed benefit both physical therapists and their patients who rely on these vital services.

And with that, Madam Chair, I yield back. And again, thank you.

*Ms. Eshoo. The gentleman yields back.

We don't have any other members that are requesting time, correct, on both sides?

Okay. I have a unanimous consent request to enter 46 documents into the record.

*Mr. Guthrie. No objection --

*Ms. Eshoo. Thank you very much.

*Mr. Guthrie. Unless they want you to read all those --

[Laughter.]

*Ms. Eshoo. No, that is all right. As long as you don't, I won't.

[The information follows:]

**********COMMITTEE INSERT**********

*Ms. Eshoo. On a serious note, in looking at this, this is really an honor roll of both individuals and organizations in our country that are weighing in.

I want to thank each one of you, the witnesses. This has been a very long legislative hearing, but 22 bills, 22 bills. And I am proud of all of the members, their work from both sides of the aisle, and each one of you, because you have added, you know, the texture, the richness, the different layers of the legislation, most, most helpful.

So you have been here for, let's see, three-and-a-half -- I would say three-and-a-half hours. You have more than earned your keep with us. So thank you to each one of you, to the staffs on both sides of the aisle of the committee.

And members do have 10 business days to submit additional questions for the record. So witnesses, we ask that you respond to promptly to any questions that are submitted to you that you receive.

So with that, with our lasting gratitude to all of you, the subcommittee is adjourned.

[Whereupon, at 2:07 p.m., the subcommittee was adjourned.]