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THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

HYBRID HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTEENTH CONGRESS

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[1] The legislation has been retained in committee files and is available at https://docs.house.gov/Committee/Calendar/ByEvent.aspx?EventID=114510.

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[2] The information has been retained in committee files and also is available at https://docs.house.gov/meetings/IF/IF14/20220317/114510/HHRG-117-IF14-20220317-SD013.pdf.

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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, DC.

The subcommittee met, pursuant to notice, at 10:34 a.m. in the John D. Dingell Room, 2123 of the Rayburn House Office Building, and remotely via Cisco Webex online video conferencing, Hon. Anna Eshoo (chairwoman of the subcommittee), presiding.

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

Also present: Representatives DeGette and Tonko

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, Oversight and Investigations 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 5 minutes for an opening statement.

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

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 eight 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:]

PREPARED STATEMENT OF HON. ANNA ESHOO

Committee on Energy and Commerce

Opening Statement as Prepared for Delivery
Of
Subcommittee on Health Chairwoman Anna G. Eshoo

Hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"

March 17, 2022

Today, our Subcommittee examines 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 thoughtful work of our Subcommittee Members in putting these bills before us.

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ARPA-H will embody the nimble spirit of the highly regarded and successful Defense Advanced Research Project Agency (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 President Biden'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 to establish an independent ARPA-H within HHS. This was a momentous first step in creating an agency that will be a beacon of hope to the American people, but our work is not yet done. 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 Reps. Upton and DeGette's Cures 2.0 legislation that they have worked 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.

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

Finally, 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.

We have a panel of industry and physician experts to advise us on these bills, as many of them previously did during our hearing on the FDA drug user fee agreements. I look forward to a highly instructive hearing on these important bills.

Ms. ESHOO. The Chair now recognizes the distinguished ranking member of the Subcommittee on Health for 5 minutes for his opening statement Mr. Guthrie.

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

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 toward 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:]

PREPARED STATEMENT OF HON. BRETT GUTHRIE

Opening Statement for the Honorable Brett Guthrie
"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
March 17, 2022
As Prepared for Delivery

Thank you to my friend, Chair Eshoo, for holding this important legislative hearing today.

We're here today to discuss proposals designed to increase American biopharmaceutical innovation, a goal that I think we can confidently all say we share. Over the past decade, more novel therapies have been approved in the United States than in 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 2021. 27 of the approved therapies were first in class drugs and 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 the 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. If CMS moves forward with this plan, access to Aduhelm and future FDA-approved Alzheimer's treatments would be restricted for Americans with intellectual disabilities, such as Down Syndrome, and patients with other neurological conditions. This could have a chilling effect on investments 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 private-sector partners. That is why I am thankful to my colleagues for including 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's known as the "Valley of Death," or the time between when a drug or a device is approved by the FDA and when it is covered by a payor.

The bill would specifically allow drug and device sponsors to share key health care economic information, including pre-clinical trial results and other important information, with health insurers and other payors before a drug or device is approved by the FDA.

This would help patients gain access to potentially life-saving 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 for these communications to occur. Codifying this guidance would instill further confidence in the marketplace and provide needed regulatory certainty to the companies and payors already engaging in these information exchanges. I encourage my colleagues to support to support H.R. 7008, which also has broad industry support.

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

These payment models could have dual benefits. This could promote greater access to some of the most expensive treatments on the market 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're talking about Accelerated Approvals. If clinical benefits are in doubt, let's focus on reforming our laws so that we only have to pay for a drug if it actually works, as opposed to stymieing access to potentially lifesaving treatments.

I look forward to continuing to work with my bipartisan colleagues in advancing this important measure. I also look forward to finding ways to advance the many proposals we're discussing today. Thank you, and I yield back.

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 5 minutes of—for an opening statement.

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

Mr. PALLONE. Thank you, Chairwoman Eshoo.

Today 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 cannot 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 8 or 9 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 Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Committee on Energy and Commerce

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

Hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"

March 17, 2022

Today, we will discuss 22 pieces of legislation to boost biomedical research and innovation, diversify clinical trials, and improve program integrity at the Food and Drug Administration.

While I do not have time to discuss every bill before us today, 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. 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 on Tuesday included $1 billion for ARPA-H. 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'd like to highlight a number of bipartisan bills introduced by members of our Committee, including another bill from Chairwoman Eshoo, 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 biomedically equivalent to their brand counterparts. 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.

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ultrasound image, or a physical sign, that is reasonably likely to predict a clinical benefit, but is not itself a clinical benefit.

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.

Patients 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 sponsor 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.

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.

As we look to strengthen program integrity at FDA and improve research and development, it is critical that we ensure we are not doing anything that could weaken FDA's gold standard for safety and efficacy. We must be mindful of FDA's resources and must always put public health and patients first. I commend all the members for introducing the bills before us today and look forward to the discussion.

Mr. PALLONE. 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.

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

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 healthcare 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 ge-

netics 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:]

PREPARED STATEMENT OF HON. CATHY MCMORRIS RODGERS

Cathy McMorris Rodgers
House Energy and Commerce Committee
Subcommittee on Health
"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
March 17, 2022
As Prepared for Delivery

INTRO

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, Chairman Pallone and my colleagues, for all the bipartisan work as we come together to reauthorize serval of FDA's user fees.

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… 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 particularly 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 from more diverse populations.

We should absolutely be building on this work.

ACCELERATED APPROVAL

The agenda today also includes my bill the 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 for 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 longer lifespan, or reduction of clinical symptoms.

Accelerated approval relies on a "surrogate endpoint" – that is still reasonably likely to predict clinical benefit.

So – instead of a drug trial for a cancer therapy having to show you live longer, the trial can show that the drug shrinks the tumors.

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 will not 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 for a better life in lifesaving research is here in America.

We want patients to have options and hope …especially when it comes to serious diseases with unmet needs.

Look at 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 we discuss my bill, the Accelerating Access for Patients Act.

Let's consider together how we can expand access to promising innovation with the appropriate guardrails in place.

ARPA-H

Before I close, I would like to specifically address ARPA-H and H.R. 5585.

I was disappointed the spending bill gave $1 billion to HHS to establish ARPA-H, which I fully anticipate will be transferred to NIH.

Just 6 weeks ago, this committee heard that in order for ARPA-H to be successful, it needed to be independent of NIH.

I raised many questions around 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's more than we spend each year on block grants to state for mental health.

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

We should all want to make sure that money for research isn't wasted but spent wisely for our shared goal for more cures.

CONCLUSION

With that, I would still emphasize there are a number of great ideas in the bills before us today, many with strong bipartisan support.

I look forward to today's discussion and moving the FDA user fee reauthorization package through committee.

Thank you and I yield back.

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 5 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, M.D.

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 one 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:]

Testimony of Dr. Ruben Mesa,
Executive Director, Mays Cancer Center at UT Health San Antonio MD Anderson
Before the House Energy & Commerce Subcommittee on Health
Hearing on "*The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
March 17, 2022

Good morning. Thank you, Chairwoman Eshoo and Ranking Member Guthrie, for the honor of participating in today's hearing and discussing the important issues you are considering in this Committee.

I am Dr. Ruben Mesa. Cancer is a thief that steals from cancer patients and their loved ones both length of life and quality of life. Indeed, cancer steals cherished memories not yet made. I am the 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.

I am the Executive Director of the Mays Cancer Center at UT Health San Antonio MD Anderson in San Antonio, Texas. As the only NCI-designated cancer center in Central and South Texas, Mays Cancer Center provides leading-edge cancer care, propels innovative cancer research, and educates the next generation of leaders to end cancer in South Texas.

I am a hematologist oncologist and a leading research expert on a group of bone marrow disorders, called myeloproliferative neoplasms or MPNs, that often lead to leukemia. Over my career, I have been the principal investigator or co-principal investigator of more than 100 clinical trials, including research that has led to four FDA-approved cancer therapies since 2011. Today, Mays Cancer Center is providing access to nearly 200 cancer clinical trials to patients in our region. Clinical trials are not a luxury for patients but are essential to us being able to provide the very best care for the cancer patients of our region.

I serve on the National Board of Directors for The Leukemia & Lymphoma Society, whose mission is to cure leukemia, lymphoma, Hodgkin's disease, and myeloma and improve the quality of life of patients and their families. LLS has invested over $1.5 billion in cancer research since its founding, and LLS-funded research has been key to advancing 75 percent of the almost 100 blood cancer-related FDA approvals over the last five years.

I also have served in leadership roles within the American Society of Hematology (ASH), the American Association for Cancer Research (AACR), and the Association of American Cancer Institutions (AACI), and I was recently named to the NCI's Clinical Trials and Translational Research Advisory Committee (CTAC).

As you may infer from that background, I am dedicated to advancing new and better treatments for cancer and that only occurs not only through advances in understanding the science of cancer but also well conducted clinical trials. This is my life's work. And that is exactly why I am so passionate about the urgent need for greater diversity in the clinical trials on which patients and doctors make their decisions about treatment.

In all my years of experience as a physician researcher, I have seen firsthand the tremendous value of improving the diversity of the patients participating in clinical trials. Because breaking down barriers to clinical trial participation not only promotes health justice: It's good science.

I'll give you one example. The community served by Mays Cancer Center is roughly 5 million individuals, of which nearly 70 percent have Hispanic heritage. Learning about differences in a cancer therapy response (either in side effects or effectiveness) between populations by race, ethnicity and other factors can teach us important scientific lessons. For example, colleagues found that a genetic variant, near the estrogen receptor 1 gene, is associated with breast cancer risk in Latinas of indigenous origins and is absent in individuals 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 participants, illustrating the urgent need to ensure the diversity of research study cohorts. This discovery could lead to new treatments that could help both Latina and non-Latina breast cancer patients. The lack of diversity across clinical trials today and the systemic underrepresentation of certain groups weaken our ability to develop new therapies that 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. As America becomes more racially and ethnically diverse, a clinical trial system that fails to enroll patients from growing demographics will not support the pace of innovation that will help us meet our potential. 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 that we don't have to accept that future. In fact, you have the power to make reforms that will help ensure patients in every part of the country have access to the clinical trial care they need, while at the same time accelerating the development of new and better treatment options for patients for decades to come.

Before you today are a handful of bills aimed at tackling these big challenges.

The DEPICT Act, H.R. 6584, would make several important reforms. 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. There is no one-size-fits-all plan to attract underrepresented groups to a trial. Instead, trial sponsors would look at the demographic groups that 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 will shape how a treatment is used in the real world. Under the DEPICT Act, if a sponsor does not meet the targets it set for itself in its initial action plan, the missing data could be gathered through a timely postmarket study.

At Mays Cancer Center, we have seen the value of intentional efforts to recruit minority populations. Years ago, we found that very few clinical studies had a pre-determined plan for maximizing participation among ethnic and racial minorities. We also realized that the barriers to participation in trials have many factors including lack of awareness or trust in clinical trials, how the trial was designed, the eligibility criteria, the burden for patients to participate as it relates to travel or complexity of participation. So, we mandated that each new trial at the Mays Cancer Center put in place a Minority Accrual Plan (MAP) that includes enrollment projections and a demographic-specific toolbox with

strategies for clinical investigators to pull from to promote enrollment.[1] Since its inception in 2013, this planning process has helped at least 50 clinical trials per year with the goal of improving enrollment. Prior to its implementation, the enrollment of Hispanics into our interventional studies was 46 percent; now it is 56 percent. Accrual of Hispanics into interventional nontreatment studies has fluctuated over the years, but in 2017 it was 59 percent.[2]

Clearly, researchers need meaningful plans to recruit and retain diverse trial populations, and we need those plans to be incorporated into clinical trial designs at the earliest stages. Thoughtful, systematic approaches like our MAP program simply are not always top of mind for trial sponsors, and the DEPICT Act would hold sponsors accountable for doing the necessary work of ensuring underrepresented groups aren't left behind and examining all aspects of trial design and conduct to diminish barriers.

The DEPICT Act would also hold FDA accountable for modernizing trial rules that too often create additional barriers to trial participation. For too long, outdated FDA rules have encouraged the delivery of nearly all trial-related care at centralized academic medical centers. Yet, we know that the time and cost of travelling back and forth from a centralized trial site is a significant burden for many patients. This is a significant challenge for our center; our catchment area includes the whole of South Texas—an area roughly the size of Pennsylvania—where a patient might be up to 350 miles away. These many burdens have an outsized impact on patients with low incomes or who have hourly and shift-based jobs who have to weigh trial participation against the impact of lost wages, job insecurity due to inflexible work schedules, lack of childcare, and increased travel costs.

The good news is that FDA has begun to rethink the traditional trial rules that promoted centralized care. In March 2020, at the beginning of the COVID-19 pandemic, FDA issued guidance on conducting trials during the public health emergency.[3] This guidance allowed certain trial services to be provided at community health facilities or in a patient's home, including the ability to utilize telemedicine to screen possible participants and have interim toxicity evaluation visits, as long as precautions were in place to ensure reliable data. We have two years of experience under these new flexibilities, and it's clear that certain standardized services such as phlebotomy, traditional diagnostic imaging tests, and vitals checks can be provided safely and accurately by community providers in many cases. Making permanent these flexibilities would dramatically reduce travel and cost burdens on patients and reduce a key barrier to trial enrollment and retention. The DEPICT Act would require FDA to gather stakeholder perspectives on the flexibilities piloted during the public health emergency and publish a report detailing which flexibilities merit permanency. This is a simple step Congress can take to hold FDA accountable for modernizing rules and regulations that can reduce travel time and costs without sacrificing trial data.

Finally, the DEPICT Act would provide critical trial enrollment and education resources to community health care providers to break down the barriers between academic trial sites and the community providers patients trust. The bill includes providing federal grants directly to community health centers

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[1] Trevino, M. et al., *The Development of a Minority Recruitment Plan for Clinical* Trials, Journal of Community Medicine & Health Education, 23 August, 2013, https://www.omicsonline.org/the-development-of-a-minority-recruitment-plan-for-cancer-clinical-trials-2161-0711.1000230.php?aid=17134

[2] Mesa R., Ramirez A., *Overcoming Barriers for Latinos on Cancer Clinical Trials,* Advancing the Science of Cancer in Latinos [Internet]. 13 Dec 2019, doi:10.1007/978-3-030-29286-7_12

[3] U.S. Food & Drug Administration, *FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards*, March 2020, Updated August 30, 2021, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

serving underrepresented groups—allowing them to hire and train trial facilitation staff and implement the IT systems necessary to seamlessly educate and enroll patients.

I cannot overstate how important it is to empower community providers to answer their patients' questions and help them navigate the process of understanding trial enrollment criteria, insurance coverage, financial assistance, and all the complexities involved in even a single trial. Research has shown that trial-skeptical patients in underrepresented groups are willing to give trials a fair shake if they can discuss all their concerns with a provider they trust.[4] In South Texas we have found including the family health expert—whoever is the "go to" person in the family, whether a nurse, pharmacist, physician, or even just a well-informed family member—along with the patient in these discussions is critical, even if this occurs through Zoom or telemedicine. And resources that help to build bridges between study investigators and community providers has the potential to encourage those providers to offer trials more often as a valuable treatment option for their patients.[5]

Another bill under consideration today, **the DIVERSE Trials Act, H.R. 5030**, 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 related digital technologies, transportation, lodging, and meals to trial participants without the threat of legal action.

In addition, the DIVERSE Trials Act would go a step further by directing FDA to work with its international counterparts to harmonize federal rules on decentralized trial designs. Harmonized regulations around the world are key to facilitating trials on rare diseases for which patient populations are so small that researchers need to conduct global trials simultaneously.

Another bill in front of the Committee today, **"Cures 2.0," H.R. 6000**, would promote the type of attention necessary to make progress in the effort to promote access to trials for underrepresented groups. Cures 2.0 would promote public awareness of trials as a treatment option, call on experts at the Government Accountability Office and within HHS to recommend actions that would promote diversity in trial enrollment, and make clinicaltrials.gov more patient-friendly.

Of course, there is no silver bullet for fixing the current lack of diversity in clinical trials. No single piece of legislation can finish the job and allow us to turn to other work. This effort will take sustained attention and a willingness to act intentionally. But the results would be life-changing: Improved outcomes 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 can 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.

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[4] Brown, F., et al., *Perceptions of Participation in a Phase I, II, or III Clinical Trial Among African American Patients With Cancer: What Do Refusers Say?,* Journal of Oncology Practice, 1 November 2013, DOI: 10.1200/JOP.2013.001039

[5] Ramirez, A., et al., *Clinical trials attitudes and practices of Latino physicians*, Contemporary Clinical Trials, July 2008, https://doi.org/10.1016/j.cct.2007.11.001

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 5 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 ten 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 two trillion in savings to patients and healthcare systems over the past ten 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 ge-

neric 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:]

Testimony of

David R. Gaugh, RPh

Senior Vice President, Sciences & Regulatory Affairs

Association for Accessible Medicines

Before the

Subcommittee on Health

of the House Committee on Energy and Commerce

"The Future of Medicine:

Legislation to Encourage Innovation and Improve Oversight"

March 17, 2022

Chairwoman Eshoo, Ranking Member Guthrie and Members of the Subcommittee:

Thank you for holding today's hearing, "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight." My name is David Gaugh and I am Senior Vice President for Sciences and Regulatory Affairs at the Association for Accessible Medicines (AAM). I am a licensed pharmacist with more than two decades of experience working in and around the generic drug industry. I also represented the industry in the initial development and in both subsequent renewals of the generic drug and biosimilar user fee agreements.

AAM and its Biosimilar Council are the nation's leading trade association for the manufacturers and distributors of FDA-approved generic and biosimilar prescription medicines. Today, generic and biosimilar medicines comprise 90% of prescriptions in the United States at only 18% of total drug spending.[1] AAM's members provide more than 52,000 jobs at nearly 150 facilities and manufacture more than 60 billion doses of generic medicines in the United States every year.[2] Our core mission is to improve lives by advancing timely access to high-quality, more affordable safe and effective generic and biosimilar medicines.

In today's testimony, I will highlight the 10-year success of the FDA's GDUFA and BsUFA programs in significantly increasing patient access to lower-cost medicines and, in turn, dramatically lowering the cost of prescription drugs for America's patients and our health care system. I will also share AAM's perspectives on the additional proposals the Committee is considering today that are most relevant to generic and biosimilar developers.

GDUFA and BsUFA aim to put FDA's generic and biosimilar drug programs 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.

This year's reauthorization marks the 10-year anniversary of both GDUFA and BsUFA. Over the past decade, these programs have substantially increased resources available to FDA to review applications. More than $4 billion in supplemental user fees

[1] AAM, "The U.S. Generic & Biosimilar Medicines Savings Report," October 2021, available at https://accessiblemeds.org/sites/default/files/2021-10/AAM-2021-US-Generic-Biosimilar-Medicines-Savings-Report-web.pdf.
[2] AAM, "A Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain," October 2021, available at https://accessiblemeds.org/sites/default/files/2020-04/AAM-Blueprint-US-Pharma-Supply-Chain.pdf.

from generic and biosimilar developers was and will be provided as a result.[3] With these resources, FDA and industry have been able to significantly increase access to more affordable generic and biosimilar medicines, resulting in more treatment options and savings for patients and the United States health care system. For example:

- FDA and developers of generic medicines were able to increase efficiencies, which increased the number of generic drug approvals, with full and tentative approvals exceeding 1,000 in fiscal years 2017, 2018 and 2019. The median number of Abbreviated New Drug Application (ANDA) approvals increased over time as a result of GDUFA I and GDUFA II.[4]

- FDA licensed the first biosimilar in 2015 and has now licensed a total of 34 biosimilars in the United States.[5] Biosimilar medicines are safe, effective and more affordable treatment options for patients than their brand-name counterparts. Biosimilars are already delivering on their promise of lower costs and expanded patient access to care with average prices of more than 40% less than their reference biologics.

- Over the last 10 years, generics and biosimilars provided more than $2 trillion in savings – including $469 billion from new generics and more than $12 billion from biosimilars – to patients and the health care system in the United States.[6]

Timely approval of the FDA user fee agreements is critical to ensuring the continued availability of lower-cost generic and biosimilar medicines. AAM and its Biosimilars Council therefore strongly support congressional reauthorization of GDUFA and BsUFA as negotiated and without changes. The GDUFA III and BsUFA III commitment letters were carefully negotiated to balance program enhancements and resource requirements provided to FDA. The agreements include a year-over-year capacity planning adjuster (CPA) that allows FDA to automatically add additional full-time equivalent (FTE) resources when increased workload criteria exceed expectations. Therefore, AAM would have concerns 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 costs beyond what was negotiated and agreed to with FDA.

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[3] AAM Analysis of FDA's FY2014 – FY2020 GDUFA and BsUFA Financial Reports and Five-Year Financial Plans (2021 Update). FDA's reports are available at https://www.fda.gov/about-fda/user-fee-reports/user-fee-financial-reports.
[4] AAM Analysis of the FDA Office of Generic Drug Annual Reports (2015-2020) and Activities Report of the Generic Drug Program (FY13-FY15, FY21). FDA's reports are available at https://www.fda.gov/drugs/generic-drugs/annual-reports.
[5] Biosimilars Council, "FDA Biosimilars Approvals," March 2022, available at https://biosimilarscouncil.org/resource/fda-biosimilars-approvals/.
[6] Ibid., AAM Generic & Biosimilar Savings Report.

With that context in mind, we appreciate the opportunity to respond to the Committee's request for our perspective on additional proposals relevant to generic and biosimilar medicines.

Enhanced Access to Affordable Medicines Act **(H.R. 6973)**

The Federal Food, Drug and Cosmetic Act (FDCA) requires generic drug labeling to be the same as the brand-name reference listed drug. If brand-name drug labeling changes while the FDA is reviewing a generic drug application, approval of the generic application may be delayed until the applicant amends its labeling to conform to the updated brand-name drug labeling. Current GDUFA performance goals allow FDA to review generic drug application labeling amendments over a three-month timeframe. Thus, brand-name labeling changes, depending on how they are timed, can delay approval of generic medicines and accordingly delay patient access to more affordable FDA-approved generic alternatives. Even after the generic obtains approval, commercial launches may also be delayed and made more costly if the generic drug developer needs to reprint labeling and repackage the drug.

Brand-name drug manufacturers sometimes try to delay competition from more affordable generic medicines by initiating late-stage labeling changes. In the first six months of 2019 alone, changes to brand-name labeling appear to have occurred within 90 days of approval on 36 ANDAs.[7] Late-stage labeling changes have also occurred on blockbuster medications, such as Advair®, resulting in significant lost savings to patients and the health care system. Findings from the U.S. Government Accountability Office (GAO) echo concerns that changes to brand-name labeling "may be strategically timed to delay approvals" or that labeling changes could be made frequently in an effort to complicate generic drug approvals.[8]

The Enhanced Access to Affordable Medicines Act (H.R. 6973), introduced by Rep. Buddy Carter (R-GA), would allow FDA to approve generic applications that would otherwise be eligible for approval but for a late-stage labeling change by the brand-name manufacturer. The generic drug applicant must agree to submit revised labeling no later than 60 days after approval. The bill also includes provisions that preclude use of the pathway if the labeling change relates to warnings. These commonsense guardrails would help ensure that the latest safety and warning information is readily available to physicians and patients. AAM believes this bill would help curb late-stage labeling changes that may be used as anticompetitive tactics to delay generic approvals. As a

[7] AAM Analysis of labeling changes that occurred on FDA-approved drugs in 2019. FDA's data are available at https://www.accessdata.fda.gov/scripts/cder/daf/.
[8] GAO, "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle," August 2019, available at https://www.gao.gov/assets/gao-19-565.pdf.

result, the bill would help ensure that patients have more timely access to lower-cost generic medicines.

Increasing Transparency in Generic Drug Applications Act **(H.R. 7032)**

Certain generic medicines, including many complex generics, are required to demonstrate "Q1/Q2" sameness with the brand-name reference listed drug (RLD). A proposed generic formulation is Q1/Q2 to its RLD if it contains: (1) the same inactive ingredients ("qualitatively the same" or "Q1"); and (2) in the same concentrations ("quantitatively the same" or "Q2"). While a brand-name drug's active ingredients are identified on the product's labeling, information about inactive ingredients is not always readily available. Generic drug applicants therefore must run tests to try to decipher the components and concentrations in the brand-name drug before submitting proposed formulations to the FDA.

When FDA determines that a proposed generic formulation does not satisfy the Q1/Q2 sameness policies, the Agency informs the generic applicant of that determination, but FDA does not disclose the ingredient at issue or any details about deviations in concentration. As a result of this lack of transparency, the generic applicant must continue to submit multiple proposed formulations through the controlled correspondence process until the Q1/Q2 criteria are satisfied. This back-and-forth between the generic applicant and the FDA is often inefficient and lengthy, requiring substantial time and resources from both parties that could be dedicated to other important priorities. It also can also lead to significant delays in competition that benefits patients.

Part of the reason for this delay is that generic applicants are limited to three formulations per controlled correspondence, which can result in generics having to submit multiple controlled correspondences before the Q1/Q2 criteria are satisfied.[9] For example, it took FDA 10 years to approve a generic competitor to AbbVie's blockbuster drug Restasis® (cyclosporine), due in part to apparent Q1/Q2 issues reflected in its cyclosporine guidance.[10] At least nine developers sought approval, with only one finally receiving approval in February 2022.

Generic approvals and launches have also been substantially delayed by late-stage reversals of Q1/Q2 determinations by FDA. Indeed, FDA has reversed previous Q1/Q2 determinations for a number of complex generic products, in some cases years after making the Q1/Q2 determination. The effects of such late-stage reversals are

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[9] FDA, "Controlled Correspondence Related to Generic Drug Development Guidance for Industry," December 2020, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/controlled-correspondence-related-generic-drug-development-guidance-industry.
[10] FDA, "Draft Guidance on Cyclosporine," October 2016, available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf.

problematic for patients and the health system: generic developers generally must start from scratch and reformulate their complex products—sometimes long after commencing their development program—which ultimately delays patient access to a high-quality, low-cost complex generics.

The Increasing Transparency in Generic Drug Applications Act (H.R. 7032), introduced by Rep. Annie Kuster (D-NH), would clarify FDA's authority to share information about ingredients and the nature of deviations in concentration with generic applicants. In doing so, it would reduce the burden on FDA and industry of compiling, reviewing and responding to controlled correspondence related to generic formulations. It would also limit FDA's ability to reverse a previous Q1/Q2 determination that a generic developer reasonably relied on in making formulation decisions. For these reasons, codifying this process would help prevent delays in generic drug approvals and facilitate complex generic competition, thereby delivering significant savings to patients in therapeutic areas where it is critically needed.

***INSPECTIONS Act* (H.R. 7006)**

Manufacturing facility inspections are an essential part of evaluating applications to market all FDA-approved pharmaceuticals, including brand-name, generic, and biosimilar medicines. When FDA does not conduct inspections in a timely manner, approvals and patient access to new treatments, as well as more affordable options, can be delayed.

During the last two years, there have been significant disruptions to the inspections program. In March 2020, FDA announced that it was suspending domestic and foreign inspections due to the COVID-19 pandemic. The Agency focused only on "mission-critical" inspections, a narrow category that does not include inspections tied to most drug applications. As the pandemic subsided in late 2021, FDA attempted to resume some domestic inspections. With the rise of the Omicron variant, however, FDA reverted to performing only mission-critical inspections and did not resume a normal domestic inspection schedule until February 2022.

These inspection disruptions have had a significant effect on our members' ability to obtain timely approval of more affordable generics and biosimilars. By FDA's account, as of the end of FY2021—the most recent data available to AAM at the time of this hearing—**52** human drug application decisions remain "delayed solely due to a pending inspection or facility assessment."[11] The tally of 52 likely underestimates the extent of the delays, as it excludes applications that might have had a minor issue unrelated to an inability to inspect. Inspections for biosimilar applicants are also impacted, including

[11] FDA, "An Update to the Resiliency Roadmap for FDA Inspectional Oversight," November 2021, available at https://www.fda.gov/media/154293/download.

biosimilars for brand-name biologics like Humira®.[12] Prompt inspection of such facilities is urgently needed.

Under existing authorities FDA has several alternatives to physically inspecting facilities, including: (1) obtaining inspection records remotely; (2) requesting information and records from applicants, facilities, and other inspected entities; (3) conducting remote interactive evaluations (real-time video interactions with facilities that cover the same ground as inspections); and (4) relying on inspections conducted by trusted foreign regulatory authorities under the Mutual Recognition Agreements (MRA). FDA, however, infrequently uses these alternatives. For example, FDA informed AAM that, as of December 2021, it had conducted **only five** remote interactive evaluations.

AAM recognizes the important role inspections play in FDA's ability to assess the overall quality of applications. Our members also share the Agency's concerns about public health and preventing the spread of COVID-19 among FDA and manufacturing facility employees. The interruptions caused by COVID-19, however, delayed and denied patients prompt access to new therapies and generic and biosimilar choices that would lower drug costs. If new COVID-19 variants emerge, or if there is a future pandemic, FDA's inspections could be paused again.

The Improving the Nation's Safe Pharmaceuticals and Excipients by Creating Tools for Inspecting and Overseeing Needed Supplies (INSPECTIONS) Act (H.R. 7006), introduced by Reps. Morgan Griffith (R-VA) and Peter Welch (D-VT), would enhance FDA's oversight of facilities that manufacture prescription drugs and would help resolve some of the issues outlined above by:

- Adding the compliance history of a facility's home country to the list of factors determining a facility's risk level;
- Authorizing FDA to use certain records to satisfy requirements for pre-approval or risk-based surveillance inspections;
- Expressly empowering FDA to enter into MRAs that cover pre-approval inspections, rather than just risk-based surveillance inspections; and
- Calling for GAO oversight on the use of alternatives to in-person inspections.

AAM commends the bill sponsors' and Committee's ongoing attention to the inspections backlog. We agree that FDA should consider expanding its MRA with the European Union, where each jurisdiction recognizes and relies on the other's inspection reports, to cover pre-approval inspections and not just post-market surveillance inspections. We also believe FDA should expand use of remote interactive evaluations and use them more frequently in place of a physical inspection, in addition to using

[12] Center for Biosimilars, "FDA Delays Review of Alvotech's AVT02 Adalimumab Biosimilar Candidate," September 2021, available at https://www.centerforbiosimilars.com/view/fda-delays-review-of-alvotech-s-avt02-adalimumab-biosimilar-candidate.

alternative tools in place of an in-person inspection to verify corrective actions for a site that had received a warning letter. Some of the provisions in this bill may encourage the Agency to take those steps, which may help reduce the backlog and prevent the situation from worsening should there be future COVID-19 variants or other public health emergencies that may hinder in-person inspections.

Given the level of disruption caused by the pandemic, however, AAM recommends the bill be strengthened by requiring FDA to evaluate alternatives when an in-person inspection is not possible. Should FDA determine that an alternative to an in-person inspection cannot be used, the Agency would be required to inform the applicant which alternatives were considered and the reasons why an in-person inspection was deemed necessary. We believe this additional transparency and accountability will encourage FDA to perform its critical mission—without delay—while preserving the Agency's discretion and judgment to require in-person inspections when necessary.

***MADE in America Act* (H.R. 3927)**

AAM and its members agree that there is a role for Congress in enhancing domestic manufacturing and the security of the supply chain. While AAM shares many of the goals of the Manufacturing API, Drugs, and Excipients (MADE) in America Act (H.R. 3927), we are concerned that this proposal—without additional appropriations from Congress—would take away critical resources from FDA as negotiated in GDUFA III.

With that said, AAM believes there are important steps Congress can and should take to ensure uninterrupted patient access to life-saving medicines now and in the future as outlined in AAM's "Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain."[13] Creating the conditions that support and encourage further investment is vital to ensuring the most critical medicines—those most essential to our country's health and security—are manufactured in the United States. In order to establish and maintain this environment, AAM's Blueprint recommends the following:

- Creating new grant, tax and other incentives to support increased domestic production of medicines on the FDA's Essential Medicines List ("essential medicines");
- Supplying the Strategic National Stockpile, the Department of Veterans Affairs and other agencies with essential medicines on a long-term basis;
- Leveraging Medicare and Medicaid to support greater domestic production of essential medicines;
- Reducing regulatory inefficiencies to streamline the federal approval for U.S.-based facilities to manufacture essential medicines; and,
- Promoting a global, cooperative approach to diversifying the supply chain.

[13] Ibid., AAM Blueprint.

The Blueprint includes actionable, short-term steps to expedite more domestic production of essential medicines, while putting in place a series of incentives to enhance the security of the pharmaceutical supply chain. Global coordination across a resilient, high-quality and reliable supply chain is an important element in ensuring the ability to respond to public health challenges and natural disasters. Modern manufacturing facilities can take five to seven years and cost up to $1 billion to build. Thus, a long-term, consistent commitment from the federal government is critical to harnessing existing manufacturing and building an expanded domestic manufacturing base in the United States.

The MADE in America Act seeks to mitigate drug shortages while incentivizing the domestic manufacturing of drugs, active pharmaceutical ingredients (API), personal protective equipment (PPE) and diagnostics by:

- Identifying barriers to domestic manufacturing;
- Enhancing intra-agency coordination with regard to compliance activities;
- Requiring comprehensive reporting on FDA's utilization of MRAs;
- Enhancing transparency of drug facility inspection timelines by building on FDA's annual facilities inspection reports; and
- Creating a new pathway for FDA to evaluate advanced manufacturing technologies.

AAM shares many of the goals of this legislation, including increasing the efficiency of FDA's regulatory and approval processes, removing redundancies and reducing the time for approvals across the board. Instead of waiting until after a facility is built and equipment is installed and validated, FDA should expand cooperation with the manufacturer, working collaboratively to evaluate and approve the facility and the tech transfer processes concurrently. To accomplish these goals, AAM believes that the creation of an FDA intra-agency working group focused on helping expedite reviews and approvals to domestic pharmaceutical manufacturing would be helpful. This working group would focus on reviewing for approval the transfer of production back into either U.S.-approved facilities or newly constructed facilities at new or existing sites, including those utilizing advanced manufacturing technology.

AAM also supports continued exploration and study of advanced manufacturing technologies, including continuous manufacturing. These technologies, however, are still relatively new and may not be viable options for all product lines and all medicines. FDA's review and validation of these technologies could be helpful in building stronger evidence for adoption in addition to increasing the efficiency of the regulatory review process. Because advanced manufacturing technologies are not always appropriate or the best option for all products, we encourage policymakers and regulators to consider the potential unintentional consequences—such as slowing down or decreasing the amount of generic competition and creating or exacerbating drug shortages—that would result

from preferencing or unintentionally steering toward manufacturing methods that may not be appropriate or feasible for various types of drugs.

While AAM shares many of the goals of H.R. 3927, we believe this legislation would require a significant increase in resources and FTEs for FDA to implement. The resource and FTE commitments under GDUFA III and BsUFA III were very carefully negotiated, with industry providing sufficient funds to implement the commitments outlined in the agreements. Enactment of these additional provisions without additional appropriations from Congress could pull from these resources, placing a strain on the remaining resources available to FDA. We encourage Congress to carefully consider imposing new requirements on FDA that would impede its ability to fulfill the negotiated commitments under GDUFA III.

***Drug Manufacturing Innovation Act* (H.R. 6988)**

AAM supports the continued exploration and study of advanced manufacturing technologies. While these technologies may hold promise, their adoption requires substantial investments in specialized chemistry and engineering expertise, the acquisition of new facilities or the conversion of existing facilities, and the potential abandonment of existing manufacturing capital that is still within its useful life. Generic developers operate in competitive and often low-margin markets. While some generic developers are exploring the costs and benefits of using advanced manufacturing technologies, these technologies may not be viable or sustainable options for certain product lines, especially for low-volume medicines.

The Drug Manufacturing Innovation Act (H.R. 6988), introduced by Reps. Mike Levin (D-CA) and John Joyce (R-PA), would establish a program to support the adoption of, and improve the development of, innovative approaches to drug product design and manufacturing. It would also require FDA to issue guidance on regulatory requirements related to the development of such technologies and the data required to support approval of drugs made pursuant to their use.

While guidance providing clear expectations for the adoption and regulatory requirements related to advanced manufacturing technologies would be helpful, preferencing the use of advanced manufacturing technologies over other methods could have a negative impact on patient access to medicines. It could have significant unintended consequences, such as creating drug shortages, increasing prices and driving generic competition out of the market. We therefore encourage any programs, working groups and guidances contemplated by this legislation to focus on increasing the knowledge base and evidence supporting use of advanced manufacturing technologies and providing direction and other helpful information to drug developers who choose to implement these technologies.

Biosimilar Interchangeability Determinations (H.R. 7047)

Biosimilars—and, by extension, interchangeables—must have the same strength as the reference product under the *Biologics Price Competition and Innovation Act* (BPCIA).[14] FDA has historically defined "strength" for parenteral solutions to mean both total drug content and concentration.[15] When FDA determines a biosimilar is interchangeable with its reference product, it may be substituted for that brand-name product under the applicable state law. To incentivize the development of interchangeable biosimilars, the BPCIA awards a period of exclusivity to the first interchangeable biosimilar for the same reference product.

H.R. 7047, introduced by Rep. Kurt Schrader (D-OR), would provide FDA with the discretion to waive the same strength requirement for biosimilars in certain cases.[16] Because biosimilarity is a prerequisite for interchangeability, this would potentially result in a biosimilar with a different concentration and a different volume than the reference product being interchangeable—and therefore eligible for substitution—with the reference product. In addition, if FDA determined a biosimilar with a different concentration from the reference product is interchangeable pursuant to this proposal, it could result in the first interchangeable biosimilar, to the extent it remains eligible for exclusivity, blocking another interchangeable product at the same concentration as the reference product from receiving interchangeable exclusivity.

We understand H.R. 7047 is trying to address short-term issues associated with product launches and anticompetitive tactics. AAM and its Biosimilars Council strongly share this goal, but we are concerned that this specific proposal does not represent the correct approach for addressing this key issue. In particular, AAM encourages the Committee to assess some of the implications from this proposal on the BPCIA as described below.

First, AAM is concerned that modifying strength and interchangeable exclusivity in this manner could lead to the gaming of exclusivity and potential dissemination of misinformation by brand-name companies to suggest that products are different. The bedrock principle underlying interchangeability—whether in the generic drug or biosimilar contexts—is that follow-on products are the same as their brand products in all ways that matter. This ensures a follow-on product can be confidently used in place of a brand without the intervention of a health care provider.

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[14] PHS Act § 351(k)(2)(A)(i)(IV); PHS Act § 351(k)(4)(A)(i).
[15] FDA, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)," December 2018, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/new-and-revised-draft-qas-biosimilar-development-and-bpci-act-revision-3, pp. 5-6 ("[A] sponsor of a proposed biosimilar product or proposed interchangeable product with an 'injection' dosage form (e.g., a solution) can demonstrate that its product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity) and the same concentration of drug substance (in mass or units of activity per unit volume).").
[16] PHS Act § 351(k)(2)(A)(i)(IV).

Second, if this proposal is added to the user fee reauthorization, it would likely be enacted right on the cusp of biosimilar competition for Humira. As AAM understands the proposal, it would result in one interchangeable for Humira—to the extent that the sponsor has not lost exclusivity—rather than two potentially simultaneous interchangeables at different strengths. Indeed, Boehringer Ingelheim currently has an interchangeability determination for its low-concentration adalimumab biosimilar[17] and Alvotech is seeking a separate interchangeability determination for a high-concentration adalimumab biosimilar.[18] As AAM understands this proposal, it could likely preclude such a second, simultaneous interchangeability determination because all strengths of Humira would be considered the same reference product for interchangeable exclusivity purposes. This may be problematic for patients: two or more simultaneous interchangeables could lead to additional competition that benefits patients and the health care system. More importantly, these potentially negative effects on competition would apply to future biologics and would not be limited to Humira.

AAM recognizes and appreciates that H.R. 7047 is intended to address problematic, competition-stifling behavior. We would be glad to work with the Committee to directly address anticompetitive tactics and to help ensure that biosimilars and interchangeables are not harmed by last-minute changes to brand-name products. We would also welcome the opportunity to discuss how Congress could take steps to reduce the clinical burden on biosimilars and interchangeable manufacturers to ensure more timely patient access to low-cost medicines. However, making significant modifications to the BPCIA will likely lead to significant unintended and unpredictable consequences for competition and access to more affordable biosimilar options.

Biologics Marketing Transparency Act **(H.R. 7035)**

The FDA Reauthorization Act of 2017 (FDARA) included provisions requiring holders of approved brand-name and generic applications to notify FDA in advance of withdrawing a drug from the market or if a drug will not be available for sale. FDA uses these marketing status notifications to update drug information listed in the Agency's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book")—and, in particular, the discontinued section of the Orange Book. Inclusion of this information in the Orange Book can help abate confusion about the marketing status of various drugs. Accurate drug marketing information is also helpful to generic drug

[17] Center for Biosimilars, "FDA Grants Interchangeable Status for Boehringer Ingelheim's Adalimumab Biosimilar (Cyltezo)," October 2021, available at https://www.centerforbiosimilars.com/view/fda-grants-interchangeable-status-for-boehringer-ingelheim-s-adalimumab-biosimilar-cyltezo-.
[18] JD Supra, "FDA Accepts Alvotech's BLA Supporting Interchangeability for ATV02, a High Concentration, Citrate-Free Biosimilar Candidate for Humira®," March 2022, available at https://www.jdsupra.com/legalnews/fda-accepts-alvotech-s-bla-supporting-6313361/.

developers because withdrawal of a brand-name drug from the market can complicate ANDA submissions and reviews, and it can delay ANDA approvals.

The Biologics Marketing Transparency Act (H.R. 7035), introduced by Reps. Kathy Manning (D-NC) and Richard Hudson (R-NC), would extend FDARA's marketing status notification requirements to biologic medicines licensed under the Public Health Service Act. This commonsense proposal will provide useful information to biosimilar developers through the Purple Book. AAM supported the 506I marketing status provision included in FDARA and we look forward to working with the Committee on this proposal to ensure that it is appropriately tailored to address biologics.

Conclusion

The proposed GDUFA III and BsUFA III performance goals presented to Congress represent a sustained collaboration among FDA, industry and other vested stakeholders. More than 14 months were spent negotiating the two packages. We are proud that the commitments reached will significantly benefit America's patients by increasing access to more affordable generic and biosimilar medicines. Many lessons have been learned from the prior two GDUFA and BsUFA agreements, and we feel strongly that, with GDUFA III and BsUFA III, we arrived at a thoughtful, carefully negotiated commitment that will help address complex issues for both the generic drug and biosimilar user fee programs. Throughout the negotiation process, we focused on increasing patient access to more affordable, high-quality generic and biosimilar medicines. We believe we were successful in that endeavor.

AAM understands that the legislative proposals under discussion today, and the reauthorization package Congress ultimately passes, could affect FDA's ability to implement the user fee agreements. It is important to balance how each of these policies may alter the allocation of resources between the negotiated user fees and the amounts appropriated by Congress each year to fund FDA's operations. Similarly, the timely approval of the user fee agreements is of paramount importance to ensuring that the generic drug and biosimilar review programs continue uninterrupted for the benefit of patient access to more affordable medicines. We look forward to working with members of both parties to ensure timely passage of GDUFA III and BsUFA III.

Thank you again for the opportunity to testify on these important proposals. I look forward to answering your questions.

Ms. ESHOO. Wonderful, thank you, Mr. Gaugh.
Next, Dr. Vereshchagina, you are recognized for 5 minutes.

STATEMENT OF LUCY VERESHCHAGINA, Ph.D.

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 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:]

Testimony of

Lucy Vereshchagina, PhD, Vice President, Science and Regulatory Advocacy
Pharmaceutical Research and Manufacturers of America (PhRMA)

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

Hearing on "THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT"

March 17, 2022

Good morning, Chairwoman Eshoo, Ranking Member Guthrie, and the Members of the Subcommittee.

My name is Lucy Vereshchagina, Vice President, Science and Regulatory Advocacy at the Pharmaceutical Research and Manufacturers of America or PhRMA. PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to researching and developing medicines that enable patients to live longer, healthier, and more productive lives. Over the past 20 years, PhRMA member companies have invested more than $1 trillion in the search for new treatments and cures, including an estimated $91.1 billion in 2020 alone.

I am pleased to appear before you today to provide PhRMA's perspective on the future of medicine and the critical role that biopharmaceutical innovation plays in delivering life-saving medicines for patients.

PhRMA's key priority remains timely reauthorization of the Prescription Drug User Fee Act (PDUFA) and the Biosimilar User Fee Act (BsUFA) prior to the expiration of these programs later this year. As PhRMA stated at the Committee's February 3rd hearing on user fees, both programs are critical for ensuring patients have timely access to lifesaving medicines. PhRMA and its member companies strongly support the PDUFA VII and BsUFA III agreements as negotiated and are committed to working closely with Congress, FDA and all stakeholders to ensure the continued success of these programs.

Both the PDUFA VII and BsUFA III 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, and that the Agency is able to keep pace with ever-evolving science and have the necessary resources to ensure a timely review of innovative drugs and biologics, as well as biosimilar and interchangeable biosimilar products. Both agreements were thoughtfully negotiated with the FDA in a transparent manner, with patient organizations and others engaging with FDA through dedicated stakeholder discussions and public meetings.

PhRMA welcomes the opportunity to discuss the various policy proposals under consideration by the Committee. However, we would be concerned with any policy proposals and legislative riders that would undermine the negotiated user fee agreements and threaten passage of PDUFA VII and BsUFA III. PhRMA therefore urges Congress to reauthorize PDUFA VII and BsUFA III in a timely manner to prevent any disruptions to these critical programs and FDA operations. Delay would threaten timely access for patients to new drugs, biologic or biosimilars and create uncertainty for FDA staff. We need to ensure that the United States retains its global leadership in biopharmaceutical innovation.

I would like to highlight a few policy areas under consideration at the hearing today. First, as the Committee is considering legislative changes to the accelerated approval pathway, it is important to note this pathway has provided timely access to treatments for HIV/AIDS, cancers, and rare

diseases, leading to better health outcomes for millions of patients. It is important to stress up front that these products are approved under the same rigorous standards of safety and efficacy as traditional approvals. Furthermore, the PDUFA VII agreement contains efforts aimed at modernizing the U.S. regulatory and drug development paradigm and improving efficiencies in drug review. For example, FDA will update their review processes to provide timelier discussions and ensure agreement with sponsors on postmarketing requirements (PMRs), including for drugs and biologics approved under the accelerated approval pathway.

The longstanding accelerated approval pathway has helped expedite the availability of more than 200 treatments for patients with serious or life-threatening diseases and where there is significant unmet medical need. PhRMA member companies are committed to providing patients with safe, effective and high-quality innovative therapies, and the accelerated approval pathway helps further that goal. It is a critical tool for patients and regulators, and the biopharmaceutical 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, is critical for continued research and development investments and providing hope to millions of Americans with rare diseases who still do not have access to FDA-approved treatments for their ailments. 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, the FDA Reauthorization Act of 2017 (FDARA), included new requirements for pediatric studies of certain molecularly-targeted oncology drugs. It also required GAO to study and report to Congress on the effectiveness of these new requirements on the development of drugs and biologics for pediatric cancer indications. As the original pediatric provisions went into effect less than 2 years ago (in August 2020), additional time is needed to fully realize the full impact on pediatric oncology drug development. PhRMA believes 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 2023.

Third, PDUFA VII will advance new and powerful tools – including novel clinical trial designs, digital health technologies, and real-world evidence – that will harness scientific advances, expedite drug development, and ultimately increase patient access to new therapies, including those with rare and pediatric diseases. The broader use of digital technologies during the pandemic has also allowed the continuation of clinical trials that otherwise may have been suspended. Further, remote or decentralized clinical trials facilitated by the use of digital health technologies can enable more diverse patient populations to participate.

Improving clinical trial diversity is a critical component in broader efforts to address deeply rooted disparities across the U.S. health care system. PhRMA and our member companies are enhancing diversity in clinical trials through a number of meaningful steps. In addition to long-standing company efforts to improve diversity in clinical trials, our members voluntarily came together to renew their focus and commitment to increasing health equity through the launch of the first-ever industry-wide principles on clinical trial diversity, held a stakeholder workshop and issued a report identifying and addressing the systemic challenges that deter Black and Brown communities from participating in clinical trials.

Making a meaningful change in clinical trial diversity requires all stakeholders including industry, patient and community organizations, medical providers, policy makers, and regulators, to work together to address the existing challenges. PhRMA shares the goal of enhancing diversity in clinical trials, but policies that would create additional mandates for sponsors would have serious unintended consequences of reenforcing rather than overcoming known barriers to participation for patients including; unfeasibly large and long studies, delayed access to medicines, or disincentives for industry to invest in highly risky therapeutic areas. Instead, stakeholders must come together to address these barriers through efforts including advancing a community-based infrastructure focused on clinical trial diversity in underserved communities.

In conclusion, PhRMA urges Congress to reauthorize PDUFA and BsUFA in a timely manner to protect against any disruptions to these critical programs. We look forward to continuing to work with the Committee, Members of Congress, and other stakeholders on these important issues. Thank you for the opportunity to provide this testimony. I would be happy to address any questions.

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 5 minutes. It is good to see you, and thank you.

STATEMENT OF CARTIER ESHAM, Ph.D.

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 dialog 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:]

Testimony of Cartier Esham, Ph.D., Chief Scientific Officer
Biotechnology Innovation Organization

House Energy and Commerce Committee Hearing:
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

March 17th, 2022

Introduction

Good morning, Chairwoman Eshoo, Ranking Member Guthrie, Chairman Pallone, 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 appreciates the opportunity to speak with you today about key priorities we believe will improve regulatory oversight and transparency, as well as enable biopharmaceutical companies to modernize the clinical development paradigm to one that is more patient-centric, efficient, and inclusive, and to develop next generation medicines that will improve the lives of patients and their families. Congress has built a strong foundation over many years that has served to expedite patients' access to safe and effective therapies. We look forward to working with this Committee to build on these efforts as we discuss proposed legislation under consideration. We also urge that the Committee proceed with the timely reauthorization of the Prescription Drug User Fee Act and Biosimilar User Fee Act to ensure the FDA is able to continue to meet its mission to protect and promote the public health.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across United States in more than 30 other nations. While our membership includes most of the large, international biopharmaceutical companies, most of our members are small biotechnology companies working on cutting-edge biomedical innovations.

Key legislation and regulatory programs like the enacted Prescription Drug and Biosimilar User Fee Acts (PDUFA and BsUFA) and 21st Century Cures Act have collectively worked to ensure effective and timely reviews, improve drug and biologics safety monitoring, enable the Agency to keep pace with medical and scientific advancements, allow for earlier and more frequent FDA-sponsor engagement to identify and resolve drug and biologic development challenges, and provide the support necessary to ensure that advanced medicines are provided to patients as quickly and safely as possible. The PDUFA and

BsUFA agreements under consideration continue to advance those goals and activities and include additional commitments that will strengthen review fundamentals, enhance accountability and transparency, ensure stable growth of successful existing regulatory programs, and foster next-generation scientific advancements.

Highlighting a few key topics that are most important to BIO, our member companies, and, most importantly, the patients we serve, we would like to emphasize the importance of promoting effective scientific dialogue between the FDA and sponsors of clinical development programs, enabling the utilization of regulatory tools that are more effective and support broader and more meaningful understandings of clinical outcomes for all patients, the incorporation of patient perspectives in clinical trials and post-approval data collection, and the necessity to provide the resources and capacity needed to meet the demands and opportunities of the digital age. The COVID-19 pandemic has shown us that decentralized clinical trials, digital health technology tools, and other innovations utilized during the pandemic have the potential to improve how we develop medicines that meet the needs of patients and greatly reduce the burden on clinical trial participants, especially for those who belong to historically underserved populations and for those who suffer from rare diseases, where clinical trial populations are small and geographically dispersed. We urge timely enactment of the PDUFA VII Commitment Letter that will continue to advance meaningful integration of the patient voice and experience into drug development and review processes, builds upon important lessons learned from the pandemic, and paves a path forward to building a clinical development paradigm that is more effective, more informative, and more inclusive. We stand ready to work with Congress on legislation that advances these priorities.

Building a New Clinical Development Paradigm: More Inclusive, More Patient Centric and More Informative About Clinical Outcomes for All Patients

BIO and its members outlined our commitment to enhancing clinical trial diversity as part of our BIOEquality Agenda launched in 2020. The COVID-19 pandemic highlighted the urgent need to remove barriers and advance solutions that enable clinical trials to be more representative of the patients being treated. Scientific advancements are providing opportunities to establish a clinical development and post-approval data collection approach that will improve our understanding of clinical outcomes for all

patients. The PDUFA VII Commitment letter will provide resources, capacity, and the development of guidance that will significantly advance regulatory certainty and promote the acceptance of real-world data/evidence (RWD/RWE) and digital health tools (DHTs) like remote monitoring devices, cell phones, and smart watches that are essential in more broadly enabling the utilization of decentralized or non-traditional clinical trial locations.

BIO stands ready to work with Congress, the Administration, and stakeholders to create a more expansive, inclusive, and sustainable clinical development ecosystem. We must advance regulatory alignment on the acceptance of innovative tools and approaches that enable increased participation in clinical trials from underrepresented communities and the ability to collect data that improve our understanding of clinical outcomes for all patients. In addition to important legislation addressing these issues that will be discussed today, BIO has provided this Committee with legislative proposals we believe are essential to removing barriers and establishing a regulatory framework that is more inclusive and representative of the patients we serve.

The lack of reliable data sources capturing U.S. demographics is a challenge that must be resolved. Incomplete or outright missing demographic data for many disease areas leads to poorly or inaccurately informed enrollment targets and action plans during drug development. While FDA regulations require sponsors to present a summary of safety and effectiveness data by demographic subgroups within their trials, it is difficult to compare this data to epidemiological data to understand whether enrollment targets are representative of the disease population. Sponsors also lack certainty regarding innovative clinical trial designs that could improve trial diversity. Traditional clinical trial designs are typically geographically centralized around academic medical centers and associated with significant burden for patients, such as multiple mandatory visits to the clinic. This creates significant challenges when recruiting individuals who are geographically dispersed, unable to travel, or unable to take leave from work. By contrast, modern trial designs that embrace innovative tools and methods, like digital health technologies, decentralized clinical trials, and RWD/RWE, have demonstrated success in facilitating trials and driving diverse enrollment throughout the COVID-19 pandemic[1], but companies currently lack a regulatory framework to leverage such techniques and tools fully.

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[1] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789002

We need to re-examine and update approaches to and criteria for the establishment of inclusion and exclusion criteria and advance approaches to data collection for approved medicines that enhance our understanding of benefits and risks for all patients and enable that information to be more transparent and available to patients and their care givers. Our proposal requires public meetings with comment periods and the publication of guidance on each of these topics that together will work to remove present-day barriers and establish a regulatory framework that promotes inclusive and representative clinical development and review processes.

To help build a more expansive, inclusive, and sustainable clinical trial network infrastructure, BIO also recommends that HHS conducts a series of public roundtable discussions that converge stakeholders from FDA, NIH, CDC, community organizations, industry, and clinical research organizations (CROs) to discuss, develop, and implement recommendations that will serve to create a more expansive and inclusive clinical development infrastructure. Roundtable discussion topics could include establishing a publicly available database of well-indexed active clinical trialists, establishing clinical trialist training programs and mentoring networks for investigators/trialists serving underrepresented communities, and establishing a publicly available database of community engagement organizations supported by NIH. HHS should also establish new or leverage existing programs for a federally funded clinical trial investigator fellowship pilot program for women, members of the LGBTQIA+ community, and racial and ethnic minorities to help increase participation of underrepresented populations in clinical trials.

To promote diversity and inclusion for workforce development in the STEM community, BIO also recommends requirements for FDA and NIH to improve transparency around hiring, retention, and promotion practices within their organizational leadership and scientific workforces. Requirements should outline clear objectives for staff and leadership diversification and include a regular reporting cadence to Congress on metrics related to progress on these objectives.

We acknowledge that removing regulatory barriers and enhancing and developing data sources and infrastructure will not address all existing barriers to inclusive clinical trial participation, including language and health literacy disparities and historical mistrust of certain clinical research tactics and ethics. We have established a website, The Power of Participation (www.ctpop.org), for patients, designed to help assess and locate clinical trial opportunities and identify patient and community

organizations they may find helpful. We remain committed to working with stakeholders across the public health spectrum to provide meaningful educational materials for all patients.

Accelerated Approval

BIO continues to strongly support the Accelerated Approval Pathway (AAP) for reviewing safe and effective therapies that address critical unmet patient needs in serious and life-threatening disease states. This pathway has proven to be very effective in addressing some of the most pressing public health needs and has been foundational to extending and saving countless lives since its enactment. As of June 2021, 269 new drugs or biologics to treat serious or life-threatening diseases or conditions with high unmet medical needs have been approved through this pathway, extending, and in certain cases, saving patients' lives by providing novel therapies earlier than would have been possible using the traditional pathway[2]. Medicines approved under this pathway must still meet FDA's well-established approval standard of safety and effectiveness. The AAP is essential to providing timely access to treatments where there is an unmet need and for patients who do not have any available treatments.

Since the AAP was established in 1992[3], the pathway has led to the approval of treatments that have significantly improved the care of patients suffering from many different diseases, including rare cancers, Human Immunodeficiency Virus (HIV), bacterial infections, multiple sclerosis, sickle cell disease, and other serious and life-threatening conditions. The AAP encourages scientific and medical advancement by allowing the use of surrogate or intermediate clinical endpoints that are reasonably likely to predict clinical benefit to support approval. Prior to the establishment of the AAP, patients with HIV recognized the need for a new pathway as the development of treatments using traditional endpoints on disease progression and death were prohibitory to providing access to much needed treatments for patients suffering from this deadly disease. The AAP enabled the approval of the first HIV/AIDS treatment based on the use of surrogate endpoints (viral load and CDR count) which served to prolong and save the lives of millions of patients.

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[2] https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals

[3] In 1992, and partially codified in 1997, FDA instituted the Accelerated Approval regulations (21 CFR 314 Subpart H and 601 Subpart E) to formalize the process for approving drugs to treat serious conditions that filled an unmet medical need based on a study of surrogate endpoints.

The PDUFA VII agreement includes commitments to further enable early engagement on what criteria are needed to support utilization of a surrogate endpoint. The Commitment Letter also includes support for the development and implementation of a Rare Disease Endpoint Advancement (RDEA) Pilot Program, which will facilitate collaboration and agreement between sponsors and FDA on appropriate efficacy endpoints that assess outcomes in these particularly vulnerable patient populations. The RDEA Pilot Program will prioritize endpoints with potential applicability to multiple diseases to maximize impact for patients. FDA will also develop their staff capacity to support the complex and intensive review work necessary to evaluate novel endpoints with a focus on the challenges of trials in small populations. These commitments will help ensure scientific rigor and advance regulatory understanding about what is necessary to support the utilization of a surrogate endpoint as a basis for approval.

The AAP also requires that sponsors conduct studies to confirm a continued demonstration of benefit and evaluation of risk. The FDA has the authority to withdraw a treatment from the market if it determines that the benefit has not been confirmed or it is determined that the risk outweighs the benefit. To ensure that the design and implementation of confirmatory trials are more effective, the PDUFA VII Commitment Letter provides avenues for earlier and timely discussions on the design of post-market requirements (PMRs), which are critical to confirming the clinical benefits of products receiving accelerated approval[4]. Both biopharmaceutical companies and FDA recognize the importance of post-marketing requirements to ensure timely availability of information on the safety and efficacy of certain therapies to patients when further post-approval studies are warranted. PDUFA VII aligns processes to ensure necessary early engagement and discussions are occurring in a manner that allow for more effective assessments of PMR needs and enable more thoughtful PMR study designs. PDUFA VII will also establish improved processes for the continued evaluation of PMRs post-approval to ensure requirements are being met and/or remain scientifically valid. The Commitment Letter will also serve to advance regulatory understandings about when and how RWE may be used to support PMRs that may significantly improve the ability to complete PMRs in a more effective and efficient manner.

Patients have consistently voiced their support of the use of AAP over the last 30 years. We have all seen how this pathway has led to more timely access to treatments that improve, extend, and save lives

[4] Sponsors planning to use surrogate endpoints as primary efficacy endpoints also gained an opportunity to consult with FDA earlier in the drug development process through Type C Surrogate Endpoint meetings established during PDUFA VI.

and has been foundational to continued advancements in the treatment of serious and life-threatening diseases. BIO looks forward to working with the Committee to ensure that the Accelerated Approval Pathway is working efficiently, effectively, and as intended.

Continuing Momentum with Pediatric Drug Development

BIO member companies are committed to advancing innovations on behalf of all patients, especially in areas of unmet medical need, which includes our commitment to pediatric patients. Drug development is a challenging endeavor for many reasons, including scientific and technical limitations. The research and development of vaccines and therapeutics for children represent some of the most challenging and important areas of drug development.

The challenges innovators face in studying and bringing forward promising medical products for children reflects the unique considerations in developing medical products for this population, which can range from neonates to adolescents and young adults. These considerations include the inherent physiological differences between adults and children, the dynamic that some diseases are different in adults and children, and challenges in designing and carrying out pediatric clinical trials. In some circumstances, a product may first be approved for an adult population, helping to advance the study and development of a product for use in children. However, bringing forward pediatric products often requires a case-by-case, not a "one-size-fits-all," approach.

PDUFA VII includes provisions to enhance drug development with the goal of advancing novel therapies for patients, including in disease areas with an unmet medical need and which have proven to be more challenging areas for developing therapies, like pediatrics. Leveraging advances in science, enhancing the application of drug development tools, and modernizing clinical trials are all important elements of continuing to strengthen and enhance the drug development paradigm to better serve patients, including in areas with unmet pediatric needs. PDUFA VII will build on the numerous provisions Congress has enacted over the years to help foster the development of promising therapies for children, including the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

More recently, the last PDUFA reauthorization bill (the FDA Reauthorization Act of 2017) included new requirements for pediatric studies of certain cancer drugs that FDA is in the process of implementing.

Pediatric drug development remains a priority for BIO and our members, and we celebrate the many successes that benefit our youngest patients stemming from their efforts. Today, we have numerous therapies with pediatric indications, including for neonates, that are making a measurable difference for these patients and their families. We have seen advancements across a range of conditions, including recent drug approvals in sickle cell, cystic fibrosis, pediatric rheumatologic conditions, and even Ebola, and we are optimistic about the breakthroughs to come. BIO looks forward to building on this progress, and we appreciate the opportunity to engage and collaborate with Congress and FDA on these important issues on behalf of the pediatric patients we serve.

Advanced Manufacturing

Advanced manufacturing technologies offer the promise of increased capacity and efficiency that can help sponsors expedite production, enhance product quality, and address shortages of medications essential to public health. As more products rely on platform technologies and more gene therapies are commercialized, our domestic manufacturing capacity and technology must keep pace with product innovation.

While innovation in new drug and biologic development has been robustly incentivized by the modern drug/biologic regulatory framework at FDA, the use of innovative manufacturing technologies and techniques has not had similar support. Many companies, especially smaller ones, often decide that making in-house investments in manufacturing, or taking a risk on a new manufacturing technology offered by a contract manufacturer, is not feasible. Once a product is approved, manufacturing processes used during the initial application become the standard for the product, because any changes require additional supplemental applications, regulatory hurdles, and product risks which have no market incentive to overcome, despite potential improvements to manufacturing efficiency and product consistency and quality.

The FDA acknowledges this barrier and recognizes that adopting innovative approaches to manufacturing may present both technical and regulatory challenges. Biopharmaceutical companies may have concerns that using such technologies could result in delays while FDA reviewers familiarize

themselves with the new technologies and determine how they may be evaluated within the existing regulatory framework[5]. Until these innovative tools and technologies "graduate" to standard regulatory frameworks, the development and review of products that leverage them is resource and time-intensive for both sponsors and the Agency.

BIO supports FDA and Congressional efforts to facilitate the development and adoption of novel manufacturing technologies such as CDER's Emerging Technology Program. The ETP aims to "promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with Emerging Technology Team (ETT) members to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission." Additional support for the ETP program would help to facilitate the development and utilization of 21st Century manufacturing technologies. A comparable program in CBER, the CBER Advanced Technologies Team (CATT), provides similar support and engagement to sponsors developing CBER-regulated products that involve advanced manufacturing and testing technologies[6].

Recently, FDA requested that the National Academies of Sciences, Engineering, and Medicine (NASEM) research and publish a consensus study report on the existing and near-future manufacturing technologies that the Agency should prepare for and the barriers that stand in the way of their adoption. The final NASEM report, published in February 2021, recommended that the agency establish a review pathway to evaluate technologies independently from individual drug product applications[7]. BIO believes such a pathway would create confidence, establish regulatory structure and consistency, and facilitate the adoption of new technologies to produce new or existing drug products.

Closing Comments

BIO strongly supports timely enactment of the PDUFA VII and BsUFA III Commitment Letters. The resources provided will serve to maintain FDA's global leadership and enable the Agency to keep pace with the medical and scientific advances of today and tomorrow. We look forward to working with

[5] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program
[6] https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt
[7] https://www.nap.edu/catalog/26009/innovations-in-pharmaceutical-manufacturing-on-the-horizon-technical-challenges-regulatory

Congress to advance proposals that support the development and implementation of a new clinical development paradigm that is more expansive, inclusive, and patient-centric and continues to incentivize the development and timely delivery of next generation medicines that improve the lives of patients and their families.

Ms. ESHOO. Thank you, Dr. Esham.

Dr. Allen, you are recognized for your 5 minutes of testimony, and welcome again, and thank you.

STATEMENT OF JEFF ALLEN, Ph.D.

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 two 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:]

THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

Testimony Before

Committee on Energy and Commerce

Subcommittee on Health

Jeff Allen, PhD

President & CEO

Friends of Cancer Research

March 17, 2022

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

Good morning, Chairman Pallone, Chairwoman Eshoo, Ranking Members McMorris-Rogers and Guthrie, and Members of the committee. I am Dr. Jeff Allen, President and CEO of Friends of Cancer Research, a cancer research advocacy organization dedicated to accelerating science & technology from bench to bedside. I would like to thank all Members and the staff of this committee for putting together this important hearing. It is an honor to testify before you today and provide our perspective on several topics included in bills being considered by the committee.

Today represents a unique opportunity to address a diverse set of issues critical to developing a new paradigm for new medicines. Over the past several years healthcare has faced unprecedented pressure on a local and global level in the form of COVID-19. While this has resulted in tragic losses and unimaginable challenges, we are now left to identify the shortcomings, build on the successes, and design a future for health that is able to protect from future pandemics, but also make much needed progress against longstanding challenges like cancer, neurological disease, and the over 6500 rare diseases that have no treatments.[1] I appreciate the opportunity to highlight several areas that will be key for progress related to research and regulation of new medical products that are being discussed today.

Supporting Innovative Research and Regulatory Infrastructure

The route to developing new medicines is long, complex and at times unpredictable. The National Institutes of Health (NIH) is the engine of discovery and enables research toward better health. The NIH

[1] Kaufmann, P, Pariser, AR and Austin, C. From scientific discovery to treatments for rare diseases – the view from the National Center for Advancing Translational Sciences – Office of Rare Diseases Research. *Orphanet J Rare Dis* 13, 196 (2018). https://doi.org/10.1186/s13023-018-0936-x

also provides a critical component of research explaining biological underpinnings of diseases and uncovering new ways to treat them. In some cases, these discoveries can translate into potential new medicines and ultimately manufactured into treatments available to patients worldwide. However, this is a process that reportedly takes upwards of 12 years and costs over $1 billion.[2]

In order to expedite typical timeframes and improve the government's capability to speed research, President Biden has proposed the establishment of the Advanced Research Projects Agency for Health (ARPA-H). With bipartisan collaboration, Congress has recently identified funds for ARPA-H and this committee has taken on the important work to authorize ARPA-H through separate legislation. ARPA-H will serve a unique role of catalyzing progress in biomedical research by focusing on transformational capabilities and proof-of-concept innovations that have broad applicability across multiple disease areas. This will enable ARPA-H to focus on different components of the biomedical research process and deploy an approach that would be distinct from other organizations. To be successful, no matter the location of ARPA-H, the independence and operational processes established through authorizing language will be key.

An additional effort to enhance infrastructure and accessibility to new medicines is through the 21st Century Cures Initiative (Cures 2.0). The proposed bill builds on numerous provisions in its predecessor that have been highly effective at promoting development and facilitating access to innovative therapies. The Cures 2.0 bill will take key steps to improve public health, support patients and caregivers, advance regulation and reimbursement, and bolster the national research infrastructure.

A specific opportunity through the Cures 2.0 bill could be to include provisions that complement the innovative regulatory programs for transformative therapies, such as the breakthrough therapy designation (BTD) and regenerative medicine advanced therapy (RMAT) designation to enable faster,

[2] Adams, CP and Brantner, VV. *Health Economics*, 19 (2010), 130–141. doi: 10.1002/hec.1454

more efficient coverage decisions to ensure Medicare beneficiaries have appropriate and timely access to new innovative treatments. A key success feature of the Breakthrough Therapy Designation has been the increased collaboration and interactions between developers and regulators to expedite the development of potentially transformative treatments for serious or life-threatening illnesses. A similar approach could be taken for qualifying technologies that may require unique payment considerations to streamline coverage decisions and enable a more seamless process between an approval by the Food and Drug Administration (FDA) and coverage determination by the Center for Medicare and Medicaid Services (CMS), where the available evidence supports such an approach.

Modernizing Clinical Trials to Promote Inclusivity and Representativeness

While efficient processes and a robust research infrastructure are necessary to support the development of new treatments for patients in need, another essential component will be modernizations to make clinical trials more inclusive, accessible, and equitable.

Barriers to the conduct of and recruitment to clinical trials present perennial challenges to the development of new medical products. For several decades, the average enrollment of adults with cancer into clinical trials has hovered around 2-8%.[3] These participation rates have been accompanied by numerous efforts to raise awareness about trials and increase educational outreach to patients and medical providers. While such efforts have likely identified many prospective participants, the criteria for determination of patient eligibility for the trials themselves have largely remained unchanged. Overly restrictive eligibility criteria can limit access to clinical trials as part of cancer care, impede

[3] Unger, JM, Hershman, DL, Till, C , et.al. When Offered to Participate": A Systematic Review and Meta-Analysis of Patient Agreement to Participate in Cancer Clinical Trials, *JNCI: Journal of the National Cancer Institute*, 113 (3), 2021 March, 244–257, https://doi.org/10.1093/jnci/djaa155

enrollment thereby slowing drug development, and cause trials to be less reflective of the patient population that will eventually use new medicines once approved.[4]

Eligibility criteria do play an important role in protecting patients and a relatively homogenous population can be beneficial when attempting to isolate the effect of a drug. However, trial eligibility criteria are often established based on past trials, rather than evaluating and prospectively designing optimal eligibility criteria based on the properties of the drug and the patient population that is being sought. This "cut and paste" approach may contribute to unnecessary exclusion of patients. and may be a barrier to inclusion of more diverse patient populations in clinical trials. For example, routine lab tests are used to identify potential confounding conditions, such as abnormal kidney or liver function, that may make trial participation potentially unsuitable for a patient. The acceptable reference ranges for normal values have been based on averages, and over the years, these averages have come from the most frequent trial participants – similarly aged Caucasian males.[5] This can effectively exclude a more diverse and representative population, whose metabolic factors may not match those historic participants, but still represent normal biologic functioning to permit clinical trial participation.

Addressing challenges due to restrictive eligibility criteria requires all stakeholders in the oncology clinical trial space to implement changes and increase opportunities for trial participation – and progress is being made. One such multi-stakeholder effort was our partnership with the American Society of Clinical Oncology (ASCO) to launch a collaborative effort alongside expert advisors from clinical research, industry, the FDA, the National Cancer Institute, and other advocacy organizations. The objective was to establish multiple subject-specific working groups to develop recommendations for ways in which

[4] Jin S, Pazdur R, Sridhara R. Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. *J Clin Oncol.* 2017 Nov 20;35(33):3745-3752. doi: 10.1200/JCO.2017.73.4186

[5] Spira AI, Stewart MD, Jones S, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. *Clin Cancer Res.* 2021 May 1;27(9):2416-2423. doi: 10.1158/1078-0432.CCR-20-3853. Epub 2021 Feb 9. PMID: 33563636; PMCID: PMC8102342.

eligibility criteria could be expanded in cancer clinical trials.[6,7] Subsequently, our findings were published in the peer-reviewed literature and informed several recently finalized FDA guidance documents on how eligibility criteria might be broadened,[8, 9, 10, 11] and updated NCI trial templates to help ensure that eligibility criteria routinely start broad and then narrow as appropriate, rather than carrying over previous trial parameters.[12] These efforts can help engage trial sponsors within the pharmaceutical industry and academic research centers to expand eligibility and take steps to not exclude potential patients who could benefit from their products.

Several of the bills included in today's hearing provide new opportunities for increased transparency and promote the inclusion of more diverse and representative enrollment in clinical trials. When looking more broadly at ways to make clinical research more accessible, eligibility criteria is just one opportunity. However, expanding the criteria for trial entry will allow more people to have access to clinical research as part of their care, allow drug developers, medical practitioners, and patients to gain insights for a more representative population, and increase the number of patients who can participate in trials. Tangible and collaborative steps to modify clinical trial constructs can help raise historic rates for trial accrual and speed up trial enrollment – ultimately resulting in new medicines making it to patients sooner.

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[6] Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, *J Clin Oncol*, 35(33): 3737-3744. DOI: 10.1200/JCO.2017.73.7916

[7] Kim ES, Uldrick TS, Schenkel C, et al. Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO-Friends of Cancer Research Joint Research Statement. *Clin Cancer Res*. 2021 May 1;27(9):2394-2399. doi: 10.1158/1078-0432.CCR-20-3852. Epub 2021 Feb 9. PMID: 33563632.

[8] FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients, https://www.fda.gov/media/121318/download

[9] FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, https://www.fda.gov/media/123745/download

[10] FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Brain Metastases, https://www.fda.gov/media/121317/download

[11] FDA Guidance: Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections, https://www.fda.gov/media/121319/download

[12] Broadening/Modernizing Eligibility Criteria for National Cancer Institute (NCI) Sponsored Clinical Trials, https://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Broadened_Eligibility_Criteria_Guidance.pdf

Optimizing the Accelerated Approval Pathway

The Accelerated Approval pathway has been an important regulatory mechanism for FDA to allow for earlier approval of safe and effective drugs that treat serious and life-threatening illnesses than would occur through the traditional approval program. The pathway allows for the approval of a drug based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. Earlier approval enables quicker access to new safe and effective drugs and is reserved for drugs that treat serious or life-threatening conditions where the risks associated with no or delayed treatment have negative consequences.

The Accelerated Approval pathway broadly applies to all drug classes and is used across clinical divisions within the FDA. However, Accelerated Approval has been most frequently used in oncology. In the past 10 years (2010- June 2021), 80% (138/168) of FDA's Accelerated Approvals were granted for oncology indications.[13] This is due in large part to the availability of measurable endpoints, such as tumor shrinkage, that can be directly associated with the activity of a drug. Cancer researchers have also made significant efforts to standardize tumor response measures which has helped ensure the consistent application of endpoints like response rates and improve in the interpretability of clinical trial results. The robust experience of Accelerated Approval in oncology, which is a unique therapeutic setting given an extensive infrastructure for conducting research and aggregating data, can be used to inform the use of Accelerated Approval in other diseases. Accelerated Approval has extended or, in certain cases, saved patients' lives through earlier access to novel therapies. One assessment of oncology treatments concluded that therapies receiving Accelerated Approval were made available a median of 3.4 years

[13] US Food and Drug Administration. CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint As of June 30, 2021. https://www.fda.gov/media/151146/download. Accessed online 09/15/2021.

earlier than if approval were based on a full clinical endpoint, such as overall survival. [14]

Products approved through the Accelerated Approval pathway are subject to post approval study requirements to verify the anticipated effect of the drug and to further characterize the associated risks and clinical benefits. Based on post approval confirmatory studies, the FDA may grant full approval to the drug or, if post approval studies fail to demonstrate benefit (or other evidence demonstrates the product is not shown to be safe and effective), the approval may be withdrawn. In evaluating the total number of indications that have received Accelerated Approval, 49.3% of all indications and 44.2% of cancer indications have been converted to full approval based upon subsequent evidence. Conversely, 9.9% of all accelerated approvals and 9.0% of oncology accelerated approvals have been withdrawn. This yields 42.8% (115/282, all indications) and 46.8% (89/190, oncology indications) that have neither been converted to a full approval or withdrawn (Table 1). Together this indicates a highly favorable success rate for confirmation of benefit and demonstrates the importance of timely post approval studies.

Table 1. Regulatory Outcomes of Accelerated Approval Drugs

Accelerated Approval Indications	Total with Accelerated Approval	Total Converted to Full Approval	Total Withdrawn	Total Pending Action
All[15]	282	139 (49.3.0%)	28 (9.9%)	115 (40.8%)
All Approved Over 5-Years[14]	66	34 (51.5%)	14 (21.2%%)	18 (27.7%%)

[14] Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. *JAMA Oncol*. 2018;4(6):849–856. doi:10.1001/jamaoncol.2017.5618. Accessed online 10/1/2020.

[15] Kaltenboeck A, Mehlman A, Pearson S. Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Costs. Apr 26, 2021. https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway- -ICER-White-Paper- -April-2021.pdf (accessed August 5, 2021).

Oncology[16]	190	84 (44.2%)	17 (9.0%)	89 (46.8%)
Oncology Products Over 5-Years[17]	33	19 (57.6%)	5 (15.2%)	9 (27.3%)

Post approval confirmatory studies are required to verify and describe the anticipated effect and to further characterize the long-term outcomes associated with the drug.[17] Because these studies require collection of additional clinical data and may involve the conduct of additional clinical trials, they require additional time for completion. For drugs that have received Accelerated Approval for oncology indications, conversion to full approval took a median time of 3.1 years, while withdrawals took 3.8 years to generate the evidence necessary for action. For the indications that have not yet been converted or withdrawn, the median time since their approval is 1.8 years (Table 2). It is important to note that because 72% (64/89) of pending oncology indications having been approved in the last 2 years, it may be unrealistic to expect their post approval studies to be completed already (Figure 1).

As technology and science evolve it's important to ensure to that the Accelerated Approval pathway continues to serve it's intended purpose. These data indicate that the Accelerated Approval pathway has enabled patients with serious diseases to have access to new medicines years earlier. Key to continued success is both early planning for when Accelerated Approval may be used, and transparency to robust post approval evidence generation. Together this will enhance confidence in the Accelerated Approval process and bolster the ability to address unmet needs for the people that need it most.

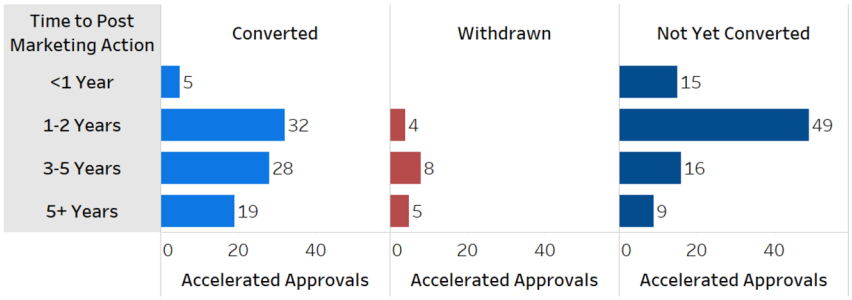
[16] Friends of Cancer Research: https://friendsofcancerresearch.org/drug-development-dashboard (accessed March 10, 2022).
[17] FDA Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics, https://www.fda.gov/media/86377/download

Table 2. Median Years between Accelerated Approval and Follow-up Action (1992-June 2021)

Accelerated Approval Indications	Converted	Withdrawn	Pending*
All (n=278)	3.2	6.9	1.8
Oncology (n=190)	3.1	3.8	1.8

*Median time calculation for Accelerated Approvals pending action = time between accelerated approval and the date of this analysis (January 31, 2022).

Figure 1. All Oncology Accelerated Approvals' Time to Follow-up Action.



Facilitating High-Quality Evidence Generation

Accelerated Approval allows patient access to therapies that have demonstrated an initial treatment effect, potentially before a randomized trial that fully establishes clinical benefit is completed. Approval prior to established clinical benefit can potentially introduce loss of clinical equipoise that may interfere with continued drug development and timely completion of post marketing requirements to confirm clinical benefit. For example, patients may be reluctant to enroll in trials where they may be randomized

to receive a perceived inferior therapy, or they may discontinue participating in ongoing clinical trials once the product is accessible on the market after it has received Accelerated Approval. Because these are real challenges encountered for drugs receiving Accelerated Approval, strategies such as earlier initiation of confirmatory trials have been pursued. Similarly, the use of alternative trial designs or leveraging data from clinical practice (real-world data) is being explored.

As previously noted, under 10% of adult patients with cancer are enrolled in a clinical trial as part of their care. Therefore, the vast majority of experience with cancer drugs occurs outside of clinical trials in typical medical practices or the so-called "real-world". Relatively recent advances in information technology and data capture have allowed for the collection of significantly more data from medical practice than historically has been available. Much of this information is collected for administrative purposes, such as billing, and is therefore not intentionally structured for research. However, real-world data could be leveraged as a research tool to generate evidence about approved medical products in widespread use.

To explore the opportunities and challenge to using real-world data for research, we partnered with several leading healthcare data organizations to characterize patient populations treated for non-small cell lung cancer and evaluate how real-world data could inform outcome measures. Through a series of collaborative pilot projects, we were able to show that it is possible to align on key data elements across different data sources and implement common study protocols. This enabled the identification of similar directionality in treatment effects for both immunotherapy and chemotherapy as had previously been seen in clinical trials.[18] While consistency and reproducibility of findings can add confidence in the results, several challenges with aligning different data sources remain that will need to be further

[18] Stewart M, Norden A, Dreyer N, et.al. An Exploratory Analysis of Real-World End Points for Assessing Outcomes Among Immunotherapy-Treated Patients with Advanced Non-Small-Cell Lung Cancer. *JCO Clinical Cancer Informatics*. 2019 July Special Article. 1-15. Doi: 10.1200/cci.18.00155.

evaluated to optimize the use of real-world data. Challenges that can make interpretation of results difficult include missing data points, differences in care patterns, variation in subsequent therapies and follow-up time, and differences in outcome measures/endpoints compared to more structured research studies.

Despite these challenges, there are significant opportunities for future utilization of real-world evidence to supplement data obtained from clinical trials. For example, data obtained from real-world practice provides important information regarding patients that differ from the relatively homogenous population that may have been included in the initial clinical trials. Real-world data can help provide insights into the impact that factors such as comorbidities, stage of disease, clinical characteristics, and demographics such as age, sex, race and ethnicity can have on outcomes.[19] While in most cases this not intended as a substitute for the data that can be developed through a traditional clinical study, with continued refinement to methodologies, real-world data will provide a growing amount of important information about the safety and effective use of medical products over time.

Conclusion

While there are certainly challenges ahead, scientific advancement has brought us to a time of great opportunity. For the people who currently depend on safe and effective medicines, for those who are holding strong for the breakthroughs to come, and for every future patient, there isn't time to waste. Through the leadership of this committee, we can enable a strong research and evidence infrastructure, implement clinical trials that are more inclusive, and ensure that avenues are available for timely access

[19] Rivera, D.R., Henk, H.J., Garrett-Mayer, E., et.al. (2022), The Friends of Cancer Research Real-World Data Collaboration Pilot 2.0: Methodological Recommendations from Oncology Case Studies. *Clin Pharmacol Ther*, 111: 283-292. https://doi.org/10.1002/cpt.2453

to promising new safe and effective medicines that can transform the lives of millions of Americans who need new treatments and cures.

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About Friends of Cancer Research

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Ms. ESHOO. Thank you, Dr. Allen.

And last, but not least, Dr. Ramachandran, for your 5 minutes of testimony. And again, thank you, and welcome back.

STATEMENT OF RESHMA RAMACHANDRAN, M.D., M.P.P.

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 toward 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 2 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 8-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 subpopulation 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:]

Written Testimony of Reshma Ramachandran, M.D., M.P.P. of Yale School of Medicine

Hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
Subcommittee on Health
U.S. House of Representatives Committee on Energy and Commerce
March 17, 2022

Chairman Pallone, Ranking Member Rodgers, and distinguished members of the subcommittee, thank you for the invitation to testify today. My name is Reshma Ramachandran. I am a physician and researcher in the National Clinician Scholars Program at Yale School of Medicine. I also lead the Doctors for America Food and Drug Administration (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. I am honored to testify before you today. My remarks reflect my own views and not that of my employers nor the organizations I work with.

As a practicing physician, FDA approval signals that the agency has undertaken a rigorous review process to ensure that the benefits of an approved treatment outweigh its risks such that it can be prescribed safely by myself and my colleagues to our patients. However, continued erosion of FDA's regulatory standards that ultimately led to the controversial approval of aducanumab for Alzheimer's disease has shaken our trust in the agency, overshadowing its laudable work during ongoing COVID-19 pandemic that has enabled the authorization and approval of multiple effective and safe vaccines, therapies, and diagnostics. Nevertheless, with the impending reauthorization of the Prescription Drug User Fee Authorization Act, there is an opportunity for Congress to recenter the FDA's role around its core mission to protect patients above all else.

In my written testimony below, I discuss only a portion of the many important legislative proposals before the subcommittee as follows:

1) ***Resetting the Balance Between Earlier Access and Ensuring Confirmation of Efficacy and Safety of Accelerated Approval Drugs***

The accelerated approval pathway is intended to provide our patients with earlier access to potentially promising new treatments based on the success of a surrogate endpoint thought to be predictive of clinical benefit.[1] In exchange for this ability to market drugs earlier to patients as granted under the accelerated approval pathway, drug manufacturers are required to complete additional postapproval studies to confirm that the drug does indeed demonstrate the predicted clinical benefit. Should the confirmatory trials fail to do so or the manufacturer fail to initiate required postapproval studies in a timely manner or initiate them at all, the FDA can withdraw marketing authorization the accelerated approval treatment. However, the lack of adequate oversight and enforcement authority by the FDA has allowed industry sponsors to continue to market these drugs and make them available for patients despite negative confirmatory trials or delays in conducting required postapproval studies.

A recent analysis by the medical journal, *The BMJ*, found that nearly half (n=112) of the 253 drugs approved through the accelerated approval pathway between 1992 and 2020 have not been confirmed to be clinically effective.[2] Of these, one-fifth (n=24) have been on the market for more than five years. Only sixteen of all accelerated approval drugs from this period were withdrawn, either due to a lack of efficacy or because the confirmatory trials were never conducted.

The application of accelerated approval for specific drug classes has also changed over time. Although accelerated approval was initially used to expedite approval of treatments for HIV/AIDS in the 1990s, the majority of drugs receiving accelerated approval over the last decade has been cancer drugs.[3] Ten of the 35 oncology indications approved through the accelerated approval pathway in the last six years were considered "dangling" accelerated approvals – that is, accelerated approval drugs where their confirmatory trials had failed to confirm clinical benefit, but continued to remain on the market, available for patients to use and clinicians to prescribe.[4] Four of these dangling approvals were voluntarily withdrawn by industry sponsors. The remaining six were discussed by the FDA Oncologic Drugs Advisory Committee (ODAC) in April 2021 when FDA convened this group of external advisors to review the data from the confirmatory postapproval studies and vote on whether to maintain marketing authorization for these drugs, despite failing to demonstrate clinical benefit. Ultimately, ODAC voted in favor of maintaining approval of four of the six indications.[5]

FDA could decide to make a regulatory decision that differs from that of their advisory committees. However, this rarely occurs.[6] In fact, one study specifically examining FDA approval decisions of oncology drugs found that discordance between the FDA's regulatory decision and ODAC vote only occurs when the agency decides to further expand access to a cancer drug with no prior occurrence of the FDA overruling ODAC's vote to limit access to oncology treatment.[7] As experts have noted, the FDA's decision to uphold the ODAC's vote to maintain a majority of the dangling acceleration approvals could have ramifications on future accelerated approvals.[3] Industry sponsors may become less likely to voluntarily withdraw their drugs even when their postapproval studies fail to confirm clinical benefit as ODAC's recommendations could signal to sponsors the likelihood of their accelerated approval drugs remaining on the market despite negative confirmatory trials.

Moreover, such a vote may have signaled to industry sponsors the acceptance of poorly designed postapproval studies. Prior studies have shown that such required confirmatory trials for accelerated approval drugs are small and short, with many lacking randomization, blinding, or concurrent controls[8] – key characteristics of well-designed clinical trials. Additionally, postapproval studies for drugs granted accelerated approval continue to rely on surrogate endpoints despite the intention for the trial to confirm clinical benefit and their initial approval having been based on a surrogate endpoint. Researchers examining cancer drugs approved by the FDA between 1992 and 2017 through the accelerated approval pathway found that over 40% used a surrogate endpoint as the basis for confirming benefit. Of these, nearly one-half used the same surrogate endpoint as the associated preapproval pivotal clinical trial.[9]

The harms of allowing manufacturers to market drugs that have failed to demonstrate clinical benefits for both patients and clinicians are manifold. First, clinicians may

unknowingly be prescribing treatments of limited or no clinically meaningful benefit to patients. For those conditions where they may be an available and proven alternative including a non-pharmacological option, 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 higher out-of-pocket payments and other beneficiaries to potentially pay higher premiums.[10]

Without a doubt, the controversial decision by the FDA to approve aducanumab for Alzheimer's disease under the accelerated approval pathway has led to significant scrutiny of this expedited review pathway. After a near unanimous vote by their independent advisory committee against aducanumab's approval, FDA allowed the sponsor to pursue accelerated approval on the basis of a surrogate marker – that is, the change in MRI findings of brain beta-amyloid, a protein hypothesized to be predictive of cognitive benefit.[11] While both pivotal trials showed a significant decrease in beta-amyloid, numerous studies have found that beta-amyloid changes do not predict clinical benefit in terms of reversing or slowing cognitive decline for patients. In fact, a review of data from more than two dozen clinical trials published in *Nature* examining beta-amyloid did not find any association with slowing or reversing the progression of Alzheimer's disease.[12] At the independent advisory committee meeting noted earlier, a senior FDA official even stated that they were not going to be using beta-amyloid "as a surrogate for efficacy."[13]

Upon approval, even FDA's biostatisticians noted that there was no evidence of association between the beta-amyloid changes and cognitive or functional changes.[11] Moreover, this surrogate marker was evaluated in only approximately a third of trial participants in both pivotal clinical trials.[14] The unusual nature of this approval has not only prompted public outcry, but also multiple investigations including by this Committee in collaboration with the House Committee on Oversight and Reform[15] as well as by the Office of the Inspector General within the Department of Health and Human Services (HHS) specifically on how FDA implements accelerated approval.[16]

In the wake of aducanumab's approval, FDA officials and legislators have since committed to reforming the accelerated approval pathway. Just last month, Dr. Robert Califf, the recently confirmed FDA Commissioner had publicly committed to Senator Ron Wyden (D-OR) that he view it as a high priority for the FDA to "ensure that drug developers granted accelerated approval conduct confirmatory trials that demonstrate that the balance of clinical benefit and risk for intended use of the drug is positive" and that these trials are "done in a timely manner."[17]

Policymakers within this committee from both sides of the aisle have introduced legislation to recenter accelerated approval to ensure a balance between timely access to new treatments for patients as well as oversight to ensure patients that these treatments are truly safe and beneficial.[18,19] Importantly, provisions within these introduced bills would allow for FDA to review and approve the design of required postapproval studies within a certain period of time that will help prevent against any delays in initiating confirmatory trials. Additionally, the bills include provisions that would allow FDA to further expedite withdrawal of accelerated approval drugs that fail their confirmatory postapproval studies or for which their postapproval studies are either delayed or not conducted. This would prevent unproven accelerated approval drugs from remaining on the market, thereby curbing any potential clinical or financial harms for patients.

Besides these important provisions, the Accelerated Approval Integrity Act (H.R. 6963) includes several additional safeguards necessary to balance faster access to potentially promising treatments and prompt confirmation of their clinical benefit. They include:

- collaboration between the FDA and the sponsor to ensure well-designed confirmatory studies with oversight of the study protocol and study completion deadline;
- submission of progress reports on the status of such postapproval studies to the FDA to ensure timely completion of confirmatory trials and assistance should there be any barriers to their completion (similar to what other national regulatory authorities in other countries such as Europe, Australia, United Kingdom, and others already require for similar approval pathways[20]);
- clear criteria for the FDA to employ in making decisions to withdraw an accelerated approval drug from the market;
- expediency in the process for FDA to withdraw an accelerated approval drug to prevent against unnecessarily prolonged marketing of unproven treatments to patients;
- automatic expiration within a specified period of time (1 year following the deadline established between the FDA and sponsor for completion of confirmatory studies; 5 years following initial accelerated approval of the drug) – again, similar to what other national regulatory authorities in other countries such as Europe, Australia, United Kingdom, and others already require for similar approval pathways[20]; and
- enforcement authority in the form of monetary penalties should sponsors fail to submit their required, routine reports on progress in completing their postapproval studies or fail to conduct such studies with due diligence.

There are also additional opportunities to further strengthen this legisation so that patients and clinicians have greater certainty of the clinical effectiveness and safety of accelerated approval treatments across the following areas:

a. Improving the Design of Required Post-Approval Studies to Truly Confirm Clinical Benefit

- **Legislation should explicitly state that postapproval studies should use clinical endpoints, not surrogate endpoints. These endpoints should be prespecified explicitly within the agreement between the FDA and the drug sponsor.**
    - Under the accelerated approval pathway, manufacturers must confirm the clinical benefit of treatments initially approved based on surrogate endpoints thought to be predictive of clinical benefit in exchange for earlier marketing authorization to patients. **In order to establish that the drug has a clinically meaningful positive outcome, sponsors should use clinical endpoints, not surrogate endpoints.** Today, a significant proportion of accelerated approval drugs continue to use surrogate endpoints as the basis for confirming clinical benefit.[9]
    - There may be "validated" surrogate endpoints that the FDA has determined after robust evaluation to be predictive of meaningful clinical outcomes. **However, at the very minimum, use of surrogate endpoints for confirmatory clinical trials**

that mirror those used for accelerated approval should not be allowed. Moreover, any surrogate endpoints used within postapproval studies should be those that are validated by the FDA. As noted earlier, nearly one-half of those cancer drugs that used surrogate endpoints to confirm clinical benefit used the *same* surrogate endpoint as in the preapproval pivotal clinical trial that led to their accelerated approval.[9]

- **FDA should draft guidance for sponsors for public comment regarding what classes of drugs or therapeutic areas for which initiating postapproval studies prior to approval may not be possible.**
    - It is understandable that FDA may need flexibility in requiring postapproval studies to be underway prior to approving a drug under accelerated approval. **However, FDA should also draft guidance for sponsors for public comment regarding what classes of drugs and therapeutic areas for which initiating postapproval studies prior to approval may not be possible.** Not only would this offer anticipatory guidance for sponsors on the drugs and diseases that the FDA will be mandating timely initiation of postapproval studies, but will also allow for public accountability by patients, clinicians, payers, and policymakers of both the agency and sponsors in implementing such requirements.
- **FDA should ensure that postapproval studies abide by existing clinical trial reporting requirements.**
    - Under the Food and Drug Administration Amendments Act (FDAAA) of 2007, sponsors are required to register clinical trials and report trial results information onto ClinicalTrials.gov.[21] **This should be reinforced specifically related to required postapproval studies for accelerated approval drugs in stating that any proposed legislation does not obviate registration and reporting commitments for such trials under FDAAA.**

b. Clarifying Use of Automatic Expiration as a Necessary Safeguard and Backstop to Prevent Patients from Receiving Unproven Treatments

- **Aligning the deadlines for automatic expiration with previously demonstrated durations for other accelerated approval drugs.**
    - The backstop of "automatic expiration" is a necessary safeguard and backstop to ensure that both patients and clinicians are not left with indefinite, continued uncertainty of the clinical benefit of an accelerated approval drug. **Nevertheless, the time period until which automatic expiration would take effect of five years as currently included in legislation should be shortened to two years after the date on which the product is approved should the required postapproval study fail to verify and describe the predicted clinical benefit or be conducted.** In examining drugs granted accelerated approval between 2009 and 2018, we found that the median postapproval study duration was 17 months.[22]

We also determined that the median time from approval to FDA-established postapproval trial results reporting deadlines for sponsors was 50 months – a median of 30 months more than the postapproval trial durations. Thus, five years may be an excessive deadline for completing confirmatory trials, particularly if FDA does require that postapproval studies are underway upon granting accelerated approval.

- Nevertheless, this concern around the length of time an accelerated approval drug remains available for patients despite continued clinical uncertainty could be mitigated by the FDA setting more prompt trial completion dates in their agreements with sponsors. However, in the case of aducanumab, the FDA granted the manufacturer 9 years to complete the required confirmatory trial, which was an outlier as illustrated in the aforementioned study. Such a prolonged deadline may have set an unfortunate precedent for future accelerated approval treatments.

c. *Strengthening FDA's Enforcement Capability to Ensure that Post-Approval Studies are Well-Designed and Completed in a Timely Manner*

- The proposed legislation includes enforcement mechanisms to ensure that sponsors of accelerated approval drugs submit required reports of their progress in completing postapproval studies and conduct these required studies with due diligence. **However, the civil monetary penalties proposed to be levied against sponsors who fail to submit such reports or conduct postapproval studies as required could be increased to match those under the FDAAA** (Section 303(f)(3)), which authorizes FDA to levy civil monetary penalties of "not more than $10,000 for each day that the violation continued after such period until the violation is corrected."[23]

d. Making Transparent FDA's Oversight of Accelerated Approval Treatments

- **FDA should make submitted progress reports of postapproval studies publicly available on the agency's website.**
  - As the drug would have been approved through the accelerated approval pathway and therefore, made available for patients in addition to the fact that the required postapproval studies are outlined within the publicly available FDA approval letter and action package, there should not be any commercially confidential information in these reports that would prevent FDA from making progress reports of such studies publicly available.
- **FDA should promptly release results from completed postapproval studies.**
  - As these accelerated approval treatments are already available for patients, it will be critical to know from a clinical care perspective what the findings of such postapproval studies are. Should the studies demonstrate no clinical benefit or benefit only in a more narrow patient population than those the drug has been indicated for, prompt availability of these results would help inform clinical care as well as practice guidelines. This may be also help mitigate any potential

therapeutic or financial harms in preventing the use or prescribing of treatments where postapproval studies are found to be negative.

- **FDA should create public and complete database of all required postapproval studies.**
    - Under this legislation, the FDA could also be tasked to update its existing searchable, public database of all postmarketing requirements to be managed in perpetuity. Importantly, the database should not remove such postapproval studies from the database once the requirement is satisfied, as currently occurs now. It should also explicitly state what the status of the required postapproval study, linked to the trial registration and results information on ClinicalTrials.gov. This information is already available to do the FDA and increasing transparency of postapproval studies would greatly benefit patients, clinicians, and researchers in determining status of individual required trials as well as such studies over time.
- **FDA should clearly state what the regulatory review process is for accelerated approval drug and other associated information regarding pivotal as well as postapproval studies within drug labels and action packages.**
    - To make clear to both clinicians and patients the evidentiary underpinning approving a treatment through accelerated approval, the FDA drug label specifically state that the product was approved based on a biomarker thought to be predictive of clinical benefit in addition to stating that the "product is subject to postmarketing studies to verify clinical benefit." Once the drug is converted from accelerated to standard approval based on positive postapproval studies, the label should be revised to clearly state what the confirmatory trial evidence is for clinical benefit.
    - Moreover, documentation regarding all drug approvals within the drug label and action package should include the National Clinical Trial (NCT) number for both preapproval and postapproval studies. Former FDA Commissioner Scott Gottlieb had announced a plan to do this,[24] but it has not yet been realized even though it would be a minor, but impactful fix.

2) Ensuring that FDA-Approved Treatments Are Tested in Trial Participants Representative of Patients Indicated

The controversial approval of the Alzheimer's disease treatment, aducanumab has also raised attention on the longstanding, neglected issue of inadequate representation of patients within clinical trials. Not only did Biogen, the manufacturer of aducanumab fail to enroll participants representative of the Medicare beneficiary population mostly likely to be prescribed this medication within its pivotal clinical trials, it also neglected to enroll participants reflective of marginalized patient populations with a disproportionate and likely, underestimated burden of Alzheimer's disease.[25] Only 0.6% (19 individuals) of participants identified as Black, 3% as Hispanic, 0.03% (1 person) as American Indian or Alaska Native, and 0.03% as Native Hawaiian

or Pacific Islander.[14] Of the 9% identified as Asian, 94% were recruited in Asia. Older Black and Hispanic adults are estimated to have Alzheimer's disease incidence up to twice or 1.5 times the rates in older White people, respectively.[26] Despite this, Biogen reported that only 6 Black and less than two dozen Hispanic people were randomized to the treatment dose approved by the FDA.[14]

Well before aducanumab, clinical trials have had limited representation from non-White race and ethnic patient populations leading to continued uncertainty among patient and clinicians of the effect of treatments across patient populations.[27,28] The FDA has proposed and taken steps to address these disparities in clinical trial enrollment, namely in 1) improving the completeness and quality of demographic subpopulation data; 2) identifying barriers to demographic subpopulation participation in clinical trials and employing strategies to encourage greater participation; and 3) making demographic subpopulation data more publicly available and transparent.[29] However, these measures have continue to fall short in moving sponsors to enroll participants of color within clinical trials. A recently published study examined data from FDA's Drug Trials Snapshots, a publicly available webpage with demographic information of pivotal trial participants for FDA-approved new molecular entities and original biologics. Although the FDA had required every pivotal trial for these drugs to include reporting of clinical benefits and risks by race, the authors found that only 20% provided such results reporting for Black patients – a figure that did not improve over the eight-year period assessed.[30]

Industry sponsors are now echoing longstanding calls to increase representation in clinical trials, issuing public statements on the importance of such measures. In response to this ongoing concern that was further brought to light with the recent approval of aducanumab, policymakers within this committee have introduced legislation to increase representation in clinical trials including the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act (H.R. 6584)[31] and the Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Act (H.R. 5030).[32]

Under the DEPICT Act, the FDA would require sponsors to take specific, enforceable actions to increase representation in clinical trials including by:

- requiring sponsors to submit as part of their applications for investigational use of drugs and devices informational on the estimated prevalence for a disease/condition the investigational drug or device is intended for, the sponsor's targets for demographic subpopulation enrollment and rationale, and "diversity action plans" for how sponsors intend to meet their intended enrollment targets;
- empowering the FDA with the authority to mandate representative postapproval studies should the sponsor fail to meet their subpopulation enrollment targets;
- allowing sponsors to receive a waiver from the FDA to not complete representative postapproval studies should they provide "sufficient justification" for why enrollment targets cannot be reached; and
- requiring the FDA to publish annual reports of progress in increasing representation in clinical trials.

Beyond the FDA, the legislation would also task the National Institutes of Health (NIH) to engage with stakeholders within "underserved communities to facilitate the inclusion of underrepresented minorities in clinical trials." Additionally, the bill would allocate grants to community health centers, often serving proportionally greater patients of color compared to other clinics, to allow them to participate in clinical trials.

Such proposed policies are long overdue towards enabling greater representation in clinical trials. Opponents to the legislation have stated that requiring sponsors to provide enrollment targets across demographic subpopulations as well as their justification, and plans to meet such enrollment targets may be too onerous for both sponsors and the FDA. However, sponsors already provide detailed information regarding their clinical trials upon registration as required under FDAAA to ClinicalTrials.gov including their overall enrollment targets, primary and secondary outcomes, clinical trial locations, and more.[33] This would be simply another necessary field for sponsors to provide to the FDA when pursuing drug or device development. The penalty for sponsors not providing such information is simply that the FDA would then require them to pursue postapproval studies examining efficacy and safety among different subpopulations. Within the legislation, FDA also has further flexibility in waiving such postapproval studies should the sponsor pursue a waiver, justifying why achieving enrollment targets may not be feasible. **To ensure that these waivers will not be pursued haphazardly by sponsors claiming to be unable to enroll diverse populations, FDA should issue guidance to clearly outline under what circumstances waiver applications would be appropriate and considered by the agency.**

There may be instances where epidemiological data regarding the prevalence of disease or condition may not be available and for which the gaps in data across subpopulations may be exacerbated by structural racism and other factors contributing to underdiagnosis among these marginalized groups. **In these situations, the FDA should set a floor for enrollment targets for clinical trials in calling for representation to reflect available national demographic subpopulation data.** Furthermore, **the legislation should also provide an opportunity for the FDA to partner with other agencies including the Centers for Disease Control and Prevention (CDC) and CMS in utilizing existing disease or condition demographic subpopulation data and to collect further data disaggregated by age, sex, and race and ethnicity.** Such data would inform sponsor's enrollment targets toward ensuring a more representative trial that mirrors that patient population who would be indicated to receive the drug or device upon FDA approval. Moreover, FDA could also include the data required under the DEPICT Act to be collected and reported for their "Annual Report on Progress to Increase Diversity in Clinical Trials and Studies" as part of annual Prescription Drug User Fee Act performance metrics.

Provisions within the DEPICT Act also allow for the use of real-world evidence to fulfill required postapproval trials. **However, the legislation should specify this further to state that such real-world evidence would be allowed solely for examining the safety and efficacy of a drug or device for which the FDA has determined that reaching enrollment targets may be difficult.** As currently written, it may be interpreted that the FDA may allow the use of real-

world evidence for any required postapproval study. As detailed in a later portion of this testimony (see Part 3 on H.R. 6000 - Cures 2.0), there are significant limitations to the use of currently available real-world evidence in being unable to feasibly replicate data collected through robust randomized controlled trials.

Other proposed legislation such as the DIVERSE Act would enable essential resources to support education, outreach, and recruitment efforts for clinical trials studying the effect of drugs and devices on diseases with a disproportionate impact on underrepresented populations. Not only would this legislation build on existing infrastructure developed during the ongoing COVID-19 pandemic to collect data including on demographics and other structural determinants of health, but it would require the FDA to issue guidance on conducting decentralized trials with "meaningful demographic diversity." Additionally, the legislation would further minimize barriers for lower-income patients, including those from communities of color to participate in clinical trials by relieving other incurred costs including for transportation or childcare.

Given that progress to date on inclusion of diverse populations into clinical trials has stalled despite FDA taking various non-enforceable measures including public reporting demographic subpopulation data of pivotal clinical trials, it is unlikely that trial sponsors will take action of their own accord without FDA oversight and enforcement capability. Thus, granting FDA the authority to require representation within clinical trials will be critical to ensuring the efficacy and safety of treatments across various demographic subpopulations are known to patients and clinicians.

3) Re-evaluating the Promises and Pitfalls of Cures 2.0

Like its predecessor, Cures 2.0 (H.R. 6000)[34] is a large legislative package containing a broad range of provisions, including a number of regulatory and financial incentives along the drug development value chain. There is no doubt that certain bill provisions would be beneficial for patients and clinicians including further allocation of funding for the study of "long COVID" or for educational awareness campaigns on the safety and importance of vaccines. However, alongside these positive proposals, Cures 2.0 also includes other provisions that would further erode evidentiary standards for FDA regulatory review, leading to continued uncertainty over whether approved drug products are truly clinically beneficial for patients. Other additional provisions would strip CMS of its discretion to review clinical trial evidence in making informed coverage and reimbursement decisions.

Specific provisions within Cures 2.0 that Congress should reconsider are:

a. Offering a Financial Incentive for Unproven Antimicrobials (PASTEUR Act)

Under the Pioneering Antimicrobial Subscriptions To End Up surging Resistance (PASTEUR) Act, manufacturers of newly-approved antimicrobials are eligible to receive as much as $3 billion payments disbursed as regular installments over a five to 10 year contract period for an individual drug. An additional $1 billion could also be allocated as an extension of the initially contracted period or given ahead of FDA approval for a promising antimicrobial drug candidate.

From these payment installations, the total cost of doses used by public payers (i.e. Medicare, Medicaid, Veterans Affairs, Indian Health Service) would be deducted. Separately and unrelated to those drugs that receive financial incentives, a federal grant program would be established through the CDC to support hospital and inpatient efforts around antimicrobial stewardship, prioritizing those hospitals in rural areas, critical access hospitals, those serving tribal populations, and safety-net hospitals. Under the PASTEUR Act, additional resources are allocated to collect and publicly report data on antibiotic use and resistance.

Although PASTEUR seemingly attempts to delink the price of newly approved antimicrobial as well as the number of doses administered from the drug's research and development costs, the multi-billion financial incentives awarded would fail to address the fundamental flaw of these new drugs. As of result of eroding evidentiary standards for approval, the FDA has approved new antimicrobials of increasingly uncertain benefit to patients. Prior characterization of pivotal clinical trials for FDA-approved antimicrobials (including a small number awarded the qualified infectious disease product or QIDP designation) between 2010 and 2015 have shown that most of these trials were noninferiority studies with none evaluating direct patient outcomes as a primary endpoint.[35]

In an ongoing research study examining the evidentiary basis for approval of QIDP indications, we found that over 20% were approved based on *in vitro* studies and a majority were tested in non-inferiority pivotal trials, which allow for intervention drugs to be less effective compared with older, effective antimicrobials by a prespecified margin.[36] Moreover, nearly half of the QIDP indication pivotal trials failed to enroll patients with potential or confirmed resistance. In fact, the FDA only confirmed efficacy against any resistant pathogens for less than a third of these indications based on their pivotal clinical trials. This suggests that these financial incentives may be misaligned, rewarding manufacturers of QIDPs for unclear effectiveness against resistant pathogens, despite receiving this special designation intended for this purpose.

Entering into such a "subscription" contract does not preclude other financial incentives. For instance, in 2019, the Centers for Medicare and Medicaid Services implemented increased new technology add-on payments and the removal of "substantial clinical improvement" criteria.[37] Therefore, should Cures 2.0 pass with the PASTEUR Act included, sponsors of new antimicrobial treatments would be eligible to not only receive $3-4 billion per drug, but also additional new technology add-on payments. This may set up a perverse situation in which health systems and hospitals would be incentivized to prescribe more of a new antimicrobial that should be conserved as a last line treatment. Moreover, as the PASTEUR Act only addresses public remuneration of new antimicrobials in the form of lump sum payments, manufacturers of these drug products would also be eligible to receive private payer reimbursement separately as additional revenue, potentially incentivizing the overuse or misuse of these new treatments.

Such financial incentives that may prompt health systems and/or hospitals to inappropriately prescribe novel antimicrobials encompassed by the PASTEUR Act would not be offset by the stewardship provisions in the bill. As written, the legislation does not tie stewardship and surveillance efforts to antimicrobials for which a "subscription" contract has been issued, making

it unclear how these treatments will be conserved in order to prevent further antimicrobial resistance.

Rather than awarding costly financial incentives for unproven antimicrobial treatments, FDA should have further discretion in granting QIDP and other expedited review pathway designations. Instead, the agency should require sponsors of antimicrobial drug candidates to conduct pivotal clinical trials in clinically relevant patient populations including those are typically excluded and that are designed to prove superiority against known, effective alternatives. Further resources should instead be allocated to address the upstream scientific bottlenecks to novel antimicrobial drug development and other alternatives such as vaccines to prevent against infections.

a. Removing CMS's Discretion in Making Coverage Decisions of Breakthrough Devices

Last year, CMS rescinded the rule regarding coverage of breakthrough devices finalized under the prior administration establishing the Medicare Coverage of Innovative Technology (MCIT) pathway.[38] Under the MCIT pathway, CMS would guarantee up to four years of coverage for FDA-designated and approved breakthrough devices. For those breakthrough devices where reimbursement rates are short of the acquisition costs, CMS would also grant new technology add-on payments, no longer considering whether the device offers substantial improvement over existing alternatives as the agency had been doing previously. Within Cures 2.0, legislators are seeking to reinstate the MCIT Pathway, codifying the removal of CMS's discretion in making coverage decisions for breakthrough devices.

Prior research examining the burgeoning Breakthrough Devices Program within the FDA found that within its first three years, high-risk breakthrough devices were approved based on trials using surrogate, short-term endpoints not clearly associated with meaningful clinical benefits.[39] Researchers also found that FDA approved some breakthrough devices without consideration of efficacy, solely relying on safety data. FDA also authorized other devices with known significant safety risks including patient death. One example they noted was that of an implantable lung valve system approved for treatment of severe pulmonary emphysema, but caused pneumothorax (i.e. lung collapse) in over a quarter of patients treated compared to none who received the usual standard of care.[39] Not only would this breakthrough device receive additional reimbursement from CMS as the agency no longer considers where it offers a substantial improvement compared to other alternatives, but under the MCIT pathway, CMS would be required to provide four years of coverage. Given that use of these devices is coupled with higher reimbursement, health systems and hospitals may be incentivized to prescribe these devices of uncertain efficacy and safety.

Moreover, FDA has had difficulty ensuring the timely completion of postapproval studies to confirm the efficacy and safety of such devices with less than 20% of required studies being completed within three to five years after FDA approval.[39] Under the MCIT Pathway, CMS would not require companies to complete such postapproval studies including those that are required as a condition of coverage.[38] Moreover, the costs of coverage under the MCIT Pathway are substantial with estimated Medicare spending on MCIT coverage for two eligible

breakthrough devices increasing from $300 million in 2021 to more than $2 billion for 14 eligible breakthrough devices. However, as researchers have pointed out, this is likely an underestimate given that over 400 devices have been designated as a breakthrough devices. Should the MCIT Pathway be instated through Cures 2.0, this would place significant financial strain on the Medicare program, possibly leading to other downstream consequences to patients in raising their health insurance premiums.

Congress must not remove CMS's discretion that protect patients, preventing them from receiving unproven and potentially unsafe breakthrough devices. Instead, legislators should require the FDA to revisit how it grants breakthrough device designation and apply more stringent conditions for this designation including mandating that sponsors meet prespecified efficacy and safety endpoints as a condition of approval. Additionally, FDA should mandate that sponsors complete postapproval efficacy and safety studies within specific periods of times. Should they fail to do so or make progress, their marketing authorization should be rescinded. Instead of guaranteeing blanket coverage for breakthrough devices of unproven benefit to patients, CMS should coordinate with FDA to incentivize completion of postapproval studies through the Coverage with Evidence Development program. Finally, CMS should apply prior discretion in awarding additional reimbursement for such devices by again applying the criteria that in order to be eligible for these additional payments, eligible breakthrough devices should demonstrate substantial improvement over other existing alternatives.

b. Inappropriately Allowing for Real-World Evidence as Adequate for Fulfilling Required Postapproval Study Requirements for Accelerated Approval Drugs

Under the 21st Century Cures Act, FDA has been examining the quality and acceptability of real world evidence (RWE) for regulatory decision-making. Cures 2.0 similarly includes such proposals for HHS to issue guidance and reports around the use of real-world evidence. The bill also would create a Real World Evidence Task Force including the HHS Secretary, CMS Administrator, FDA Commissioner, NIH Director, additional federal representatives, and private sector representatives. **Such a Task Force should also include independent representatives without financial ties to the pharmaceutical or biotechnology industries including consumer advocacy organizations and other public sector stakeholders as well as academic experts.**

Cures 2.0 also allows for RWE to be used to fulfill required postapproval studies for accelerated approval drugs. However, allowing for the use of such RWE sources may be premature and could further contribute to the clinical uncertainty of such treatments. My colleagues examined whether it would be feasible to use such RWE to emulate FDA-required postapproval confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.[40] Of the 50 confirmatory trials required by the FDA for these drugs, none could be feasibly emulated using currently available RWE sources in terms of medical claims or structured electronic health record data. This suggests that currently available RWE sources and observational methods are unlikely to replace postapproval confirmatory trial requirements as has been proposed. Other research has raised questions on the feasibility of using real world evidence to support certain regulatory decisions. One study found that only 15% of US-based

clinical trials published in high-impact medical journals could be feasibly replicated using the RWE sources of administrative claims or electronic health records data.[41]

When RWE has been used to emulate randomized controlled trials, it has underscored several complexities in designing such studies. One recently published study used medical claims data to emulate a randomized controlled trial examining the cardiovascular risk of prostate cancer treatment.[42] Only one-quarter of real-life patients using the tested treatments met the randomized controlled trial's narrow inclusion and exclusion criteria. Additionally, the study authors were unable to use RWE to precisely emulate the endpoints examined within the randomized-controlled trial. Other considerations for designing such studies include the ability to assess follow-up with available RWE as well as appropriate statistical analyses as such data is not as well controlled as in traditional clinical trials.

Already, the FDA has been taking steps to carefully understand these complexities to identify appropriate study designs and characteristics for using RWE and the agency should invest in further research with public stakeholder engagement to clearly outline appropriate use conditions for RWE in making regulatory decisions. This should be done ahead of further statutory mandates that may preclude the agency's scientific and public health discretion in determine where RWE has been shown to benefit patients. **Moreover, just as sponsors of clinical trials are required under law to publicly register their studies, submit trial protocols, and report results information on ClinicalTrials.gov,[33(p11)] sponsors of RWE studies should also be mandated to do the same – a provision that could be included as part of the Cures 2.0 package.**

4) Ensuring the American Public a Fair Return on their Public Investment Through ARPA-H

Finally, legislators have proposed establishing the Advanced Research Projects Agency for Health (ARPA-H)[43], modeled after the more flexible, nimble approach adopted by the Defense Advanced Research Projects Agency (DARPA) within the Department of Defense. The focus of this agency would be take a high-risk, high-reward approach to innovation to develop "high-need cures" in collaboration with other agencies including NIH, CMS, FDA, Biomedical Advanced Research and Development Authority (BARDA), National Center for Advancing Translational Sciences (NCATS), and more. Building on the success of significant public investment, both in terms of funding and resources, that have led to the successful, rapid development of novel COVID-19 vaccines, therapeutics, and diagnostics, ARPA-H would similarly allocate funding and other resources to addressing diseases of unmet medical need and burden among the American population.

Public investment has long since played a catalytic role in enabling transformative innovation. Studies have shown that NIH has contributed to the discovery and development of all 356 new drugs approved by the FDA between 2010 and 2019.[44] However, this figure is likely a significant underestimate of taxpayer contribution given the number of agencies beyond NIH engaged in drug development. Moreover, researchers have also found that public investment plays an outsized role in funding truly transformative health technology innovation.[45] Additionally, the

public sector is increasingly funding late stage clinical trials, particularly for more novel therapies including biologics and gene therapies.[46,47,48]

Despite such public investment, access and affordability have largely been an afterthought in this innovation model. Today, nearly 40% of adults report difficulty affording the medications we prescribe.[49] Even with COVID-19 mRNA vaccines and therapeutics where the federal government contributed funding and resources for the discovery, development, and manufacturing of these products, procurement of doses were at prices set well above marginal cost leading to record-breaking profits for manufacturers.[50] Not only do manufacturers have control of the price for these publicly-funded health technologies, but also the supply, which has contributed to significant disparities in access that has only prolonged the ongoing pandemic.[51,52] In the case of the COVID-19 mRNA vaccine manufactured by Moderna, the U.S. government financed nearly 100% of its development and continues to subsidize ongoing R&D of variant-specific and other vaccines that will be marketed by the company. The ongoing patent dispute between the NIH and Moderna highlights yet another failure with this innovation model of doling out blank checks to private and public sector partners such as universities without conditions to enable access and affordability, even during a public health emergency.[53]

Without safeguards in establishing this new agency, ARPA-H will only repeat mistakes of the past in forcing taxpayers to pay multiple times to access the results of publicly-funded research. **Legislation creating this new agency must incorporate access and affordability as part of ARPA-H's innovation model, not as an afterthought when it may be too late.** Such safeguards should include:

- a publicly-available portal of all funding and resources allocated through ARPA-H including of clinical trial costs;
- adherence to NIH's recently adopted data-sharing policy to promote open science approaches and collaboration to more effectively steward public resources and prevent against unnecessary replication;
- timely release of funded trial registration and results information including through ClinicalTrials.gov as mandated under FDAAA;
- use of non-exclusive licenses for all publicly-funded health technologies to enable competition to lower prices and enable adequate supply;
- allocation of funds for end-to-end public discovery, development, manufacturing, and distribution of health technologies for therapeutic areas of unmet need and not viewed as commercially promises by the private sector such as antimicrobials or rare diseases; and
- investment in building a robust pipeline of researchers from communities of color.

References:

1. Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. FDA. Published June 15, 2019. Accessed January 31, 2022. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review

2. Mahase E. FDA allows drugs without proven clinical benefit to languish for years on accelerated pathway. *BMJ*. 2021;374:n1898. doi:10.1136/bmj.n1898

3. Powell K, Lythgoe MP, Prasad V. The Oncologic Drugs Advisory Committee Votes of April 2021—Implications for the Fate of Accelerated Approval. *JAMA Oncology*. 2021;7(11):1607-1609. doi:10.1001/jamaoncol.2021.3046

4. Beaver JA, Pazdur R. "Dangling" Accelerated Approvals in Oncology. *New England Journal of Medicine*. 2021;384(18):e68. doi:10.1056/NEJMp2104846

5. Center for Drug Evaluation and Research. Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting. FDA.gov. Published April 27, 2021. Accessed March 15, 2022. https://www.fda.gov/media/150755/download

6. Zhang AD, Schwartz JL, Ross JS. Association Between Food and Drug Administration Advisory Committee Recommendations and Agency Actions, 2008–2015. *The Milbank Quarterly*. 2019;97(3):796-819. doi:10.1111/1468-0009.12403

7. Haslam A, Gill J, Prasad V. Oncology Drug Advisory Committee Recommendations and the US Food and Drug Administration's Actions. *Mayo Clinic Proceedings*. 2020;95(2):424-426. doi:10.1016/j.mayocp.2019.12.002

8. Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636. doi:10.1001/jama.2017.9415

9. Gyawali B, Hey SP, Kesselheim AS. Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval. *JAMA Internal Medicine*. 2019;179(7):906-913. doi:10.1001/jamainternmed.2019.0462

10. Gyawali B, Rome BN, Kesselheim AS. Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study. *BMJ*. 2021;374:n1959. doi:10.1136/bmj.n1959

11. Alexander GC, Knopman DS, Emerson SS, et al. Revisiting FDA Approval of Aducanumab. *New England Journal of Medicine*. 2021;385(9):769-771. doi:10.1056/NEJMp2110468

12. Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019;15(2):73-88. doi:10.1038/s41582-018-0116-6

13. Food and Drug Administration. Peripheral and Center Nervous System Drugs Advisory Committee Meeting. Published online November 6, 2020. Accessed January 29, 2022. https://www.fda.gov/media/145691/download

14. Center for Drug Evaluation and Research. Clinical Review(s): Aduhelm (aducanumab). Published online June 7, 2021. Accessed August 10, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf

15. House Committee on Energy and Commerce. Chairs Pallone and Maloney Announce Investigation of Biogen's Alzheimer's Drug Aduhelm. Democrats, Energy and Commerce Committee. Published June 25, 2021. Accessed March 15, 2022. https://energycommerce.house.gov/newsroom/press-releases/chairs-pallone-and-maloney-announce-investigation-of-biogen-s-alzheimer-s

16. U.S. Department of Health and Human Services. Review of the FDA's Accelerated Approval Pathway. Office of the Inspector General. Published August 4, 2021. Accessed March 14, 2022. https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp

17. Califf R. Califf letter to Wyden on Accelerated Approval. Published online February 8, 2022. Accessed March 12, 2022. https://www.finance.senate.gov/imo/media/doc/020822%20Califf%20letter%20to%20Wyden%20on%20Accelerated%20Approval.pdf

18. Pallone F. *Accelerated Approval Integrity Act of 2022*.; :8.

19. Rodgers CM. *Accelerating Access for Patients Act of 2022*. Accessed March 15, 2022. https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BILLS-117hr6996ih.pdf

20. Mehta GU, de Claro RA, Pazdur R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. *JAMA Oncology*. Published online January 20, 2022. doi:10.1001/jamaoncol.2021.6854

21. Ramachandran R, Morten CJ, Ross JS. Strengthening the FDA's Enforcement of ClinicalTrials.gov Reporting Requirements. *JAMA*. Published online November 12, 2021. doi:10.1001/jama.2021.19773

22. Wallach JD, Ramachandran R, Bruckner T, Ross JS. Comparison of Duration of Postapproval vs Pivotal Trials for Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval, 2009-2018. *JAMA Network Open*. 2021;4(11):e2133601. doi:10.1001/jamanetworkopen.2021.33601

23. Food and Drug Administration. Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. Published online August 2020. Accessed August 18, 2021. https://www.fda.gov/media/113361/download

24. Office of the Commissioner. FDA Commissioner Scott Gottlieb, M.D., on new steps FDA is taking to enhance transparency of clinical trial information to support innovation and scientific inquiry related to new drugs. FDA.gov. Published March 24, 2020. Accessed March 15, 2022. https://www.fda.gov/news-events/press-announcements/fda-commissioner-scott-gottlieb-md-new-steps-fda-taking-enhance-transparency-clinical-trial

25. Manly JJ, Glymour MM. What the Aducanumab Approval Reveals About Alzheimer Disease Research. *JAMA Neurology*. 2021;78(11):1305-1306. doi:10.1001/jamaneurol.2021.3404

26. *Special Report - Race, Ethnicity, and Alzheimer's in America*. Alzheimer's Association; 2021. Accessed August 10, 2021. https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report.pdf

27. Oh SS, Galanter J, Thakur N, et al. Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. *PLOS Medicine*. 2015;12(12):e1001918. doi:10.1371/journal.pmed.1001918

28. Varma T, Wallach JD, Miller JE, et al. Reporting of Study Participant Demographic Characteristics and Demographic Representation in Premarketing and Postmarketing Studies of Novel Cancer Therapeutics. *JAMA Network Open*. 2021;4(4):e217063. doi:10.1001/jamanetworkopen.2021.7063

29. *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data*. Food and Drug Administration; 2014. Accessed March 15, 2022. https://www.fda.gov/media/89307/download

30. Green AK, Trivedi N, Hsu JJ, Yu NL, Bach PB, Chimonas S. Despite The FDA's Five-Year Plan, Black Patients Remain Inadequately Represented In Clinical Trials For Drugs. *Health Affairs*. 2022;41(3):368-374. doi:10.1377/hlthaff.2021.01432

31. Eshoo A. *Diverse and Equitable Participation in Clinical Trials Act.*; :24. https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BILLS-117hr6584ih.pdf

32. Ruiz R. *Diversifying Investigations Via Equitable Research Studies for Everyone Trials Act*. Accessed March 15, 2022. https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BILLS-117hr5030ih.pdf

33. National Institutes of Health, Department of Health and Human Services. *PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION.*; 2017. Accessed August 17, 2021. https://www.ecfr.gov/

34. Upton F, DeGette D. *Cures 2.0 Act*. Accessed March 15, 2022. https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/BILLS-117hr6000ih.pdf

35. Deak D, Outterson K, Powers JH, Kesselheim AS. Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration–Approved Antibiotics, 2010–2015. *Ann Intern Med.* 2016;165(5):363. doi:10.7326/M16-0291

36. Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. Published online November 2016. https://www.fda.gov/media/78504/download

37. *Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospitals*. Centers for Medicare and Medicaid Services; 2019. https://www.federalregister.gov/documents/2019/08/16/2019-16762/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the

38. Rathi VK, Johnston JL, Ross JS, Dhruva SS. Medicare's New Device-Coverage Pathway — Breakthrough or Breakdown? *New England Journal of Medicine*. Published online March 10, 2021. doi:10.1056/NEJMp2101874

39. Johnston JL, Dhruva SS, Ross JS, Rathi VK. Early experience with the FDA's Breakthrough Devices program. *Nat Biotechnol.* 2020;38(8):933-938. doi:10.1038/s41587-020-0636-7

40. Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. *JAMA Network Open*. 2021;4(11):e2133667. doi:10.1001/jamanetworkopen.2021.33667

41. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. *JAMA Network Open*. 2019;2(10):e1912869. doi:10.1001/jamanetworkopen.2019.12869

42. Wallach JD, Deng Y, McCoy RG, et al. Real-world Cardiovascular Outcomes Associated With Degarelix vs Leuprolide for Prostate Cancer Treatment. *JAMA Network Open*. 2021;4(10):e2130587. doi:10.1001/jamanetworkopen.2021.30587

43. Eshoo A. *Advanced Research Project Agency–Health (ARPA-H) Act.*; :23.

44. Cleary EG, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010–2016. *PNAS*. 2018;115(10):2329-2334. doi:10.1073/pnas.1715368115

45. Kesselheim AS, Tan YT, Avorn J. The Roles Of Academia, Rare Diseases, And Repurposing In The Development Of The Most Transformative Drugs. *Health Affairs*. 2015;34(2):286-293. doi:10.1377/hlthaff.2014.1038

46. Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. *BMJ*. 2019;367:l5766. doi:10.1136/bmj.l5766

47. Nayak RK, Lee CC, Avorn J, Kesselheim AS. Public-sector Contributions to Novel Biologic Drugs. *JAMA Internal Medicine*. 2021;181(11):1522-1525. doi:10.1001/jamainternmed.2021.3720

48. Kassir Z, Sarpatwari A, Kocak B, Kuza CC, Gellad WF. Sponsorship and Funding for Gene Therapy Trials in the United States. *JAMA*. 2020;323(9):890-891. doi:10.1001/jama.2019.22214

49. Nguyen A. Survey: How Has COVID-19 Affected Americans' Ability to Afford Their Medications? The GoodRx Prescription Savings Blog. Published March 22, 2021. https://www.goodrx.com/blog/survey-covid-19-effects-on-medication-affordability/

50. Ramachandran R, Dhodapkar M, Ross JS, Schwartz JL. Future of covid-19 vaccine pricing: lessons from influenza. *BMJ*. 2021;373:n1467. doi:10.1136/bmj.n1467

51. Ramachandran R, Ross JS, Miller JE. Access to COVID-19 Vaccines in High-, Middle-, and Low-Income Countries Hosting Clinical Trials. *medRxiv*. Published online July 22, 2021:2021.07.16.21260509. doi:10.1101/2021.07.16.21260509

52. United Nations Development Program. Global Dashboard for Vaccine Equity - Vaccine Access. UNDP Covid-19 Data Futures Platform. https://data.undp.org/vaccine-equity/accessibility/

53. Ramachandran R, Rizvi Z. Opinion | Will Moderna Ever Learn to Share? MedPage Today. Published November 28, 2021. https://www.medpagetoday.com/opinion/second-opinions/95877

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 5 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 [continuing]. 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 overrepresented in African Americans, multiple myeloma——

Ms. ESHOO. Right.

Dr. MESA [continuing]. 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 5 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 appears at the conclusion of the hearing.]

Mr. GUTHRIE. OK, 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. OK, 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 5 minutes of questions.

Mr. PALLONE. 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 fi-

nancial 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.

Mr. PALLONE. 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.

Mr. PALLONE. Now, I think you mentioned the use of real-world evidence, so just—there is only 30 seconds, but——

Dr. RAMACHANDRAN. Yes.

Mr. PALLONE [continuing]. 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.

Mr. PALLONE. 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 5 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 ten 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-threat-

ening 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 [continuing]. 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 toward 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.

OK, we now are going to recognize the gentleman from North Carolina, Mr. Butterfield, for your 5 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.

First, 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 healthcare.

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 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 [continuing]. 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 [continuing]. 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 diver-

sity. I will soon be introducing legislation with other colleagues Robin Kelly, Tony Cárdenas, 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 [continuing]. 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 [continuing]. 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 [continuing]. 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 [continuing]. Fred. OK, 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 3 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 decisionmaking. 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 referred to appears at the conclusion of the hearing.]

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. OK, it is a pleasure to recognize the gentlewoman from California, Ms. Matsui, for your 5 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—data.

Ms. ESHOO. So ordered.

[Material submitted for inclusion in the record follows:]

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 OK.

Ms. MATSUI. OK. 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 1 year or 5 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, last, 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, is this correct doesAccelerated 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, OK, a trial might take longer than the 5-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 5 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 3d, 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, Barragán, 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 short-

falls 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. OK, 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 5 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 followup 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 5 minutes.

Mr. BILIRAKIS. Thank you, Madam Chair——

Ms. ESHOO. Good to see you.

Mr. BILIRAKIS [continuing]. 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, ten 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 [continuing]. 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 5 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 healthcare 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 5 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 decisionmaking 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 5 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 1930's, 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 5 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 healthcare 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 decisionmaking.

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 2-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. OK. Well, you have to smile, right?

The Chair is very pleased to recognize the gentlewoman from Illinois, Ms. Kelly, for your 5 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 sorrya clear measurable diversity goals, and the funding application process, and have these goals be enforced 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 toward 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 followup 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 followups, 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 5 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 [continuing]. Some time soon.

Ms. ESHOO. OK, great. There is your 5 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 seven 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, OK?

Mr. CARTER. Thank you. Thank you.

Ms. ESHOO. Wonderful. All right. Dr. Ruiz of California, you are recognized for 5 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 healthcare, 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 subspecialized 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. Barragán, for your 5 minutes of questions.

Ms. BARRAGÁN. 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 suffi-

ciently 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. BARRAGÁN. What do you think the consequences are for limiting the use of accelerated approval?

Dr. ALLEN. I am sorry, can you repeat that?

Ms. BARRAGÁN. 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. BARRAGÁN. 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 followup 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 followup with you.

Ms. BARRAGÁN. OK, 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 5 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. OK, 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 5 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, fosters the 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?

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 healthcare 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.

Last, 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 Energy and Commerce colleague, Representative Curtis, for working so diligently on this bill.

And I am also looking forward to passing the FDA user feed 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 toward 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 [continuing]. 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 [continuing]. 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 guidance 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 5 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 ad-

dress 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 [continuing]. 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 5 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 toward 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 Barragán 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 healthcare?

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 toward 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 5 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 the important 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? OK. 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 5 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 2 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. Cárdenas, good to see you, and you have 5 minutes.

Mr. CÁRDENAS. 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. CÁRDENAS. 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 alter-

natives 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 healthcare.

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

Mr. CÁRDENAS. 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 healthcare 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. CÁRDENAS. 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 [continuing]. You are recognized for 5 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 Cárdenas, was talking about the Clinical Trial Diversity Act, which is such an important key. And in 21st Century Cures we started that movement toward 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 inno-

vation 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 5 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 healthcare 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?

OK. 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 appears at the conclusion of the hearing.]

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 ten 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.]

[Material submitted for inclusion in the record follows:]

March 16, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
U.S. House of Representatives

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
U.S. House of Representatives

Dear Chairwoman Eshoo and Ranking Member Guthrie:

I write to thank you for including H.R. 2565, the FDA Modernization Act, in your hearing, "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight." Along with my co-leads, Reps. Elaine Luria, Nancy Mace, Mikie Sherill, and Brendan Boyle, I ask for your favorable consideration of this legislation. As you know, the bill would amend the Federal Food, Drug and Cosmetics Act of 1938 to eliminate the animal testing mandate. In 2022, this Depression-era requirement is out-of-touch with the pace of technology. I am grateful for the bipartisan support H.R. 2565 has received from Members of the full committee.

Our drug development paradigm needs a reboot, and this bill moves us in that direction in one simple but meaningful way. It will help drive non-animal test methods in safety and efficacy testing for new drugs. Animal tests, in large part, are not predictive of the human response to drugs, with very high failure rates when the drugs go to clinical trials. Adverse drug reactions are the fourth highest cause of death in the U.S.

As I've pointed out in earlier remarks about this bill, Congress writes legislation not just for today, but for 10 or 20 years down the road. Innovation in the years ahead will almost certainly produce superior methods to animal testing in nearly all cases. The intent of the FDA Modernization Act is to allow these new technologies and strategies to be used for the benefit of people.

Let me remind you that the FDA and the pharmaceutical companies all embrace the "Three Rs" approach to animal testing – Reduction, Refinement, and Replacement. The FDA Modernization Act allows the government and pharmaceutical companies to act on their pledges. Without lifting the animal-testing requirement, the Three Rs approach is just rhetoric, not reality. Primates, beagles, and millions of animals will continue to suffer for a broken drug development paradigm that is a throwback to the first half of the 20th century.

There are currently non-animal methods for testing skin irritation, eye irritation, phototoxicity, skin sensitization, reproductive and developmental toxicity, mutagenicity, and other endpoints. Congress can remove confusion about whether these methods can be exclusively used in the pre-clinical testing phase of drug development. There are many other methods that are also remarkably promising, including Organs on Chips and Computer Modeling. For instance, in one

recent study, researchers assessed the performance of 780 human Liver-Chips across a set of 27 known hepatotoxic and non-toxic drugs. The study demonstrated that the Emulate Liver-Chip was able to correctly identify 87 percent of the tested drugs that caused drug-induced liver injury in patients despite passing through animal testing.

This bill has been endorsed by a number of stakeholder groups, including the Center for a Humane Economy, the Center for Responsible Science, Beyond Celiac, United Leukodystrophy Foundation, Myositis Association, Reflex Sympathetic Dystrophy Syndrome Association, National Hemophilia Association, National Medical Foundation, and National Hispanic Medical Association, among others.

H.R. 2565 has 30 Republican and 30 Democrat cosponsors and counting, including bipartisan Members of this Committee. I hope you will ultimately report it favorably and include it as a part of the final User Fee Amendments.

Sincerely,

Vern Buchanan
Member of Congress

AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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- PETA Switzerland
- PETA Netherlands
- PETA Foundation (U.K.)

March 16, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Testimony of

People for the Ethical Treatment of Animals

In Support of H.R. 2565 / S. 2952, "FDA Modernization Act of 2021"

Before the Subcommittee on Health, Committee on Energy and Commerce

Thursday, March 17, 2022

The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

People for the Ethical Treatment of Animals (PETA) and our more than 6.5 million supporters strongly support the FDA Modernization Act.

Many of the tests required by the U.S. Food and Drug Administration (FDA) were developed 70 years ago—long before we had organs-on-a-chip, three-dimensional tissue models, supercomputers, and artificial intelligence. The replacement of animal tests with new tools that reliably promote human health and safety is a cornerstone of 21st century FDA policy.[1,2,3] FDA initiatives like the Innovative Science and Technology Approaches for New Drugs Pilot

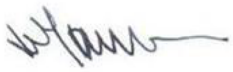
[1] FDA. "FDA's Predictive Toxicology Roadmap." Available at: https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap
[2] National Toxicology Program. "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States." Available at: https://ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy/index.html
[3] FDA. "Advancing New Alternative Methodologies at FDA." Available at: https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative- methods-fda

Program[4] and the Medical Device Development Tools program[5] are helpful steps in non-animal method implementation, and we strongly support the agency's introduction of these avenues that provide test method developers with a systematic approach that they can follow to bring modern animal-free test methods to the agency's attention. These programs, though, do not have the capacity to respond quickly to every testing area where technology is available that may improve the FDA's ability to identify safe and effective new medical treatments.

HR 2565/S 2952 takes a critical step to reinforce the FDA's commitment to adopting modern science. Despite the agency's development of policies and guidance that emphasize the value of developing non-animal tests, the restrictive language in the FFDCA—written decades before nonanimal tests were in development—continues to suggest that the FDA expects companies to rely on animal tests and does not acknowledge the extensive development of human relevant, animal-free test methods that are currently available.[6] Looking to the future, this foundational conflict between the agency's current policies and the legislation that authorizes that FDA's authority will continue to be a barrier to scientific innovation.

This bill provides statutory authority that is essential for both the FDA and the industry regulated by the FDA to adopt modern science by clearly noting that non-animal test methods—including cell-based assays, organs-on-chips and microphysiological systems, sophisticated computer modeling, and other human biology–based test methods—can be used to show that new treatments are safe and effective. The FDA's ability to adopt modern scientific knowledge is crucial, given that about 95% of new drugs that pass the currently required preclinical animal tests fail in humans, and 10 to 15 years are generally needed to bring a new therapy to market under the existing approach that relies on extensive animal testing.[7] By moving away from a reliance on animal tests while shifting toward modern, human-relevant techniques, the FDA will bring safer and more effective drugs to the public in a timely manner.

Sincerely,



Jeffrey Brown
Science Advisor

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[4] FDA Center for Drug Evaluation and Research. Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program. Available at: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

[5] FDA Center for Devices and Radiological Health. Medical Device Development Tools (MDDT). Available at: https://www.fda.gov/medical-device/science-and-research-medical-devices/medical-device-development-tools-mddt

[6] National Toxicology Program. "Alternative Methods Accepted by US Agencies." Available at: https://ntp.niehs.nih.gov/whatwestudy/niceatm/accept-methods/index.html

[7] National Institutes of Health. National Center for Advancing Translational Sciences. "About the National Center for Advancing Translational Sciences." Available at: https://ncats.nih.gov/about

Statement for the Record
National Organization for Rare Disorders

"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
Subcommittee on Health
Committee on Energy and Commerce
March 17, 2022

Chairwoman Eshoo, Ranking Member Guthrie and Members of the Health Subcommittee, the National Organization for Rare Disorders (NORD) appreciates the opportunity to provide this statement for the record for the hearing "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

Founded in 1983, NORD represents over 300 different rare disease patient organizations and the 25-30 million Americans living with a rare disease. We are committed to identifying, treating, and curing rare disorders through programs of education, policy, research, and patient services.

NORD appreciates the efforts of Congress, the FDA and negotiating parties in advancing a strong Prescription Drug User Fee Act (PDUFA) VII Commitment Letter and the efforts to reauthorize PDUFA before its current authorization expires September 30, 2022. Despite the significant progress made possible by the passage of the Orphan Drug Act of 1983 and previous PDUFA agreements, rare diseases remain an area with significant unmet need. Over 90% of the estimated 7,000 known rare diseases still do not have an FDA-approved treatment indicated for their specific rare disease.[1] Therefore, we support the approaches outlined in the PDUFA VII Commitment Letter to facilitate drug development, as well as timely review by FDA to ensure more treatment options are available to address the needs of rare disease patients. It is critically important that Congress reauthorize PDUFA, and the other user fee programs before their current authorization expires.

Beyond the PDUFA VII Commitment Letter, NORD has identified several policy priorities for consideration as part of the PDUFA reauthorization that would help ensure a regulatory environment capable of addressing the tremendous unmet needs of the rare disease community.

Support Strengthening the Accelerated Approval Pathway

The accelerated approval pathway has proven to be a vital tool in bringing safe and effective treatments to patients with rare disorders. Many facets of rare diseases make them particularly difficult to study in clinical trials targeting direct clinical benefit. For example, the number of patients with a rare condition can be small and heterogeneous, with highly diverse clinical manifestations and a long timeframe for disease progression. Furthermore, there is often a lack of prior clinical studies and a limited number of clinical investigators and treatment centers

[1] Jennifer Huron, *New Study Investigates the Number of Available Orphan Products, Generics and Biosimilars,* Nat'l Org. for Rare Disorders (Mar. 25, 2021), https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/.

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knowledgeable about a given rare disorder. This makes accelerated approval, and the ability to use surrogate endpoints in the approval process, a particularly important tool for the development of treatments for rare diseases.[2]

However, the pathway faces mounting criticism from a variety of stakeholders who have raised concerns about the accelerated approval pathway. Critics of the accelerated approval pathway claim that these treatments have yet to demonstrate clinical benefit and should therefore be treated differently because they have been studied using surrogate endpoints and are not yet "clinically proven." Some critics have characterized accelerated approval drugs as "experimental." These criticisms of the accelerated approval pathway misunderstand the law and regulations that govern it.[3] Accelerated approval—both as it is set forth in law and in regulations—does not alter FDA's gold standard of substantial evidence of safety and effectiveness.[4] To the contrary, accelerated approval is granted based on FDA's finding that a drug is safe and effective for its intended use— the same approval standard used for traditional approval.[5]

Furthermore, Congress and the FDA have considered – and rejected – the notion that accelerated approval is a different or lesser standard than traditional approval. In fact, while codifying the accelerated approval pathway in 2012,[6] Congress acknowledged the vital role the accelerated approval pathway serves for patients with rare diseases and expressed their hope that it would bring life-saving drugs to the market expeditiously.[7] Congress also affirmed FDA's conclusion that accelerated approval did not create a different standard for drug approval, stating in a "Sense of Congress" Congressional understanding that accelerated approval "may result in fewer, smaller, or shorter clinical trials... without compromising or altering the high standards of the FDA for the approval of drugs."[8]

Still, NORD believes the accelerated approval pathway could benefit from certain reforms, that if implemented, would both help to alleviate payer concerns and support continued robust patient access to these FDA approved treatments. In a June 2021 white paper, FDA's Accelerated Approval Pathway: A Rare Disease Perspective, NORD outlined several recommendations to improve the pathway.[9] Such recommendations include:

Post-market Confirmatory Study Transparency
Post-market confirmatory studies are already a condition of accelerated approval but requiring more robust and frequent reports on manufacturers progress on their confirmatory studies would give all stakeholders more confidence that these confirmatory studies are being done with due

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[2] U.S. Food & Drug Admin., CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint (Jan. 14, 2021), https://www.fda.gov/ media/88907/download
[3] 57 Fed. Reg. at 58944
[4] 57 Fed. Reg. at 58944.
[5] *Id.*
[66] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112–144, §§ 803, 901(b), 902(a), 126 Stat. 993, 1079, 1083–87 (2012)
[7] See H.R. Rep. 112-495, *35–36 (2012)
[8] See 158 Cong. Rec. H3825-01, H3848 (2012).
[9] Temkin E, Trinh, J. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. October 2021. https://rarediseases.org/wp-content/uploads/2021/06/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf

diligence. Reports should compare actual progress on the milestones that the manufacturer agreed to at the time of accelerated approval and explain where progress is falling short of the agreement. The FDA should also be required to make the information contained within these reports easily accessible to the public by putting them on the FDA's website.

Use of Real-World Evidence for Conversion to Traditional Approval
The FDA already utilizes real world evidence (RWE) in the post-market setting to evaluate safety and we believe that the utilization of RWE in the post-market to evaluate efficacy is often appropriate and should be considered. Consideration of RWE as part of the evaluation of whether the drug has an effect on the intended clinical benefit would permit FDA to convert accelerated approval drugs to traditional approval, when scientifically appropriate, at an earlier point in time.

Expedited Withdrawal of an Accelerated Approval Product
It can be difficult to design, enroll, and complete post-marketing confirmatory studies for rare disease drugs and there are frequently legitimate reasons for delays in converting a product from accelerated approval to traditional approval. However, delayed confirmatory studies also give fodder to critics of accelerated approval who claim they are a result of an inability by FDA to properly address or enforce action against accelerated approval products that have not proven clinical benefit. Clarifying the circumstances under which the expedited withdrawal of an accelerated approval product would be appropriate is important for building confidence in the pathway. However, it also critical that some flexibility be retained by the FDA in the event sponsors are pursuing conversion to traditional approval with due diligence but are falling behind on established milestones and targets.

Increased Funding and Resources for FDA
Many of these proposals would require additional, targeted resources at FDA. An increase in federal funding and resources through budgeting and appropriations could provide FDA with the resources necessary to implement some of the reforms contemplated and to exercise its existing and ideally expanded authorities when appropriate.

FDA approval is only the first step to a patient obtaining access to a treatment. True access is achieved when patients can get their treatments prescribed and affordably covered by their health program or insurer. NORD looks forward to working with Congress to ensure this pathway remains a viable way for patients to obtain access to FDA approved treatments for their rare condition at the earliest possible time.

Support Optimizing Patient Focused Drug Development

NORD appreciates that the Commitment Letter continues FDA's focus on incorporating the patient voice into the drug development and regulatory review processes. Through our work assisting Member Organizations planning several externally-led Patient-Focused Drug Development (EL-PFDD) meetings, and our own work directly coordinating several EL-PFDDs, NORD has seen firsthand the transformative impact for the patient communities in hosting PFDDs. Patients are the ultimate experts of their disease because they live with it every day.

NORD has had the opportunity to assist in planning and conducting several externally-led PFDD meetings, including one on Pyruvate Kinase Deficiency in September 2019 and on Krabbe Disease in October 2020. FDA has a special Memorandum of Understanding (MOU) with NORD and in collaboration with their Office of Patient Affairs, NORD has jointly conducted 12 Patient Listening Sessions with review divisions across CBER and CDER on a variety of disease states. Shortly after the COVID-19 pandemic began, NORD helped facilitate two special public FDA listening sessions with the rare disease community at large regarding COVID-19 and drug shortages, personal protective equipment, and participation in research and clinical trials. NORD has worked to bring the patient community together for these meetings, and, as we have learned, both the patients and FDA benefit.

The virtual and in-person meetings for rare disease communities to share directly with FDA continue to be critical and galvanizing, providing researchers, drug developers, and FDA with a robust understanding of unique patients' and caregivers' experiences with their disease and treatments. NORD welcomes provisions in the Commitment Letter to increase the utilization of PFDD, including the draft guidance on the use and submission of patient preference information for regulatory decision making. Currently, patient data is inconsistently collected and can have limited value in regulatory decision making. Changing this paradigm to ensure robust, fit-for purpose patient data is consistently collected will increase the value and utility of patient data within the FDA review process.

Opposition to H.R. 1730, the Speeding Therapy Access Today Act of 2021

Although supportive of the intent of the Speeding Therapy Access Today Act (H.R. 1730), NORD is concerned about the unintended consequences that might ensue. The establishment of an intercenter institute for rare diseases would create a burdensome requirement for the establishment of an additional, unnecessary bureaucratic structure within FDA. Rare diseases are heterogeneous and affect every system of the body, which renders them not easily centralized into a center of excellence. NORD believes the priority should instead be ensuring expert reviewers are embedded in all of the review divisions with rare disease responsibilities and that this work is appropriately resourced. Furthermore, the Agency just completed a reorganization of the Office of New Drugs in the Center for Drug Evaluation and Research (CDER). As part of the reorganization, there is more collaboration across the Agency to streamline review for rare disease products.

To the extent one of the goals of H.R. 1730 is to enhance collaboration across the Agency, there are many efforts currently underway. Examples of intercenter and interagency communication include:

- The Rare Disease Drug Development Council, a CDER led collaboration aimed at creating a forum for intercenter communication about rare disease drug development issues or learnings from difficult solutions that is joined by many across the Agency;
- The Rare Disease Council, an Office of Orphan Product Development (OOPD) led interagency council to discuss rare disease issues with different Centers and Offices at FDA;

- European Medicines Agency/Health Canada/FDA Rare Disease Cluster Call, an interregulator group from the US, European Union, and Canada, which discusses issues that lend themselves to international collaboration and harmonization;
- The Zebragram, a CDER led internal newsletter that provides relevant information on topics like novel trial design, patient engagement strategies, recent approvals, and other information related to rare disease work to the Agency;
- The Rare Disease Consult Service, a CDER led FDA-wide internal consulting service that provides guidance to review divisions regarding drug development issues common to rare diseases, including endpoints and trial designs; and
- Disease area workgroups, which are Agency-wide small groups that meet on specific diseases area issues that arise during development or review, many of which often have rare disease considerations that contribute to the complexity of the issue.

In an April 2021 meeting with the Alliance for a Stronger FDA, then-acting Commissioner Woodcock expressed similar concerns about this approach. She described the stress the Agency is under and stated, "[t]hese major or even minor structural reorganizations take a couple of years to get in place and then you have to socialize them and make sure everyone plays together well and learns to work within the new systems." She concluded by saying "the last thing I think we need to do right now – our people are tired and they …. have a wall of work in front of us that has to be gotten through – is to do a lot of very disruptive things."[10] Reorganizations are often resource intense, years-long efforts that require a substantial amount of logistical planning and preparation and requiring a further restructuring of the Agency at this point would detract from this good work already being done at the FDA with respect to rare diseases.

Support Expanding Clinical Trial Diversity

Ensuring that clinical trials appropriately represent the intended patient populations is priority for NORD. We applaud several members of the Energy and Commerce Committee for advancing ideas to expand clinical trial diversity. This is a critically important issue and can be a challenge with rare diseases as they usually have much smaller clinical trials due to the limited number of eligible patients.

Many different issues – including geographic, linguistic, cultural, and socio-economic factors – exist that tend to reduce diversity in clinical trials and lead to unfortunate inequities for patients. The NORD Rare Disease Centers of Excellence program consciously aims to address those factors, to make clinical trial enrollment easier and more equitable. The network features 31 sites in multiple states, which should present patients with opportunities to enroll in clinical trials closer to their homes and serve diverse populations in a variety of regional settings. Many of the centers already have experience and programs devoted to reaching out to medically underserved communities in their region, enabling us to reach patients with a variety of backgrounds, such as:

- Black communities, both urban and rural, who may have a strong mistrust of clinical research due to historical and sadly even more recent unethical medical research.

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[10] https://pink.pharmaintelligence.informa.com/PS144153/Woodcock-COVID-Is-Not-The-Time-For-Structural-Changes-At-US-FDA

- New immigrants and undocumented immigrant communities who, in addition to language and medical coverage barriers, may fear exposing themselves or family members to a perceived risk of increased scrutiny by US Citizenship and Immigration Services.
- Rural communities who tend to have a lower socio-economic status, limited access to health care facilities and/or to health insurance.

To increase the chances of overcoming these challenges regardless of where in our country a patient is located, NORD intends to identify best practices for community outreach and for equitable clinical enrollment at the centers where such practices have already been developed. We will share those best practices across all the centers, to increase the ease and the diversity of enrollment in clinical trials across the network and throughout the country.

Conclusion

Chairwoman Eshoo and Ranking Member Guthrie, thank you for the opportunity to submit this statement for the record and for your efforts to ensure the FDA has the resources and oversight it needs to review and approve new and innovative therapies for rare disease patients. NORD looks forward to working with you and your staff to see PDUFA VII signed into law in a timely manner and effectively implemented to benefit the rare disease community. For more information, please contact Heidi Ross, Acting Vice-President of Policy and Regulatory Affairs at HRoss@rarediseases.org.

Chairwoman Eshoo and Ranking Member Guthrie,

As the lead Democrat sponsor for H.R. 2565, the FDA Modernization Act, I ask for your favorable consideration of this measure. It is appropriate that the Subcommittee consider this reform measure as you examine "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight." This is a commonsense bill that deserves your active and determined support.

The terms set forth in the Federal Food, Drug, and Cosmetics Act require animal testing for pre-clinical testing for drug safety and efficacy. That is an outdated practice in any innovative industry but is especially anachronistic in the domain of scientific testing and drug development. Withholding authorization of non-animal methods of testing forces the FDA to default to using testing strategies that are less effective. The essence of the FDA Modernization Act is that it expands the toolbox of drug testing strategies.

The FDA Modernization Act does not eliminate animal testing in any manner; it eliminates the animal-testing mandate, allowing best science to be applied in the realm of drug development. Currently, I am not aware of any key drug development stakeholder that opposes this bill. Dozens of patient advocacy and animal welfare groups have expressed support.

I have heard from concerned citizens about their opposition to using dogs, primates, and other animals in testing protocols. We should be enthusiastically endorsing the idea of avoiding harm to animals when we can do so. Congress did so when it reauthorized the Toxic Substances Control Act in 2016 for chemical safety testing overseen by the U.S. Environmental Protection Agency.

Using 80-year-old testing strategies has not made us safer. We still do not have cures for so many major disease scourges. Adverse reactions to drugs are the fourth leading cause of death in the U.S. Drugs that pass muster for safety and efficacy in animal tests fail 90 to 95 percent of the time in human clinical trials. These are jarring and alarming facts and we should heed them. The only conclusion one can draw from these peer-reviewed conclusions is that the current animal-testing construct has its own obvious flaws.

I am proud to lead this bill with Reps. Vern Buchanan, Mikie Sherrill, Nancy Mace, and Brendan Boyle. It is one of the few bills in Congress with more than just a handful of cosponsors that has an even number of Democrats and Republicans cosponsoring it. I thank many Members of this committee for cosponsoring it as well.

I hope you will report it favorably and include it as a rider to the User Fee Amendments.

February 25, 2022

The Honorable Anna Eshoo
2367 Rayburn House Office Building
Washington, DC 20515

The Honorable Brian Fitzpatrick
271 Cannon House Office Building
Washington, DC 20515

The Honorable Robin Kelly
2416 Rayburn House Office Building
Washington, DC 20515

RE: The Diverse and Equitable Participation in Clinical Trials (DEPICT) Act

Dear Representatives Eshoo, Fitzpatrick, and Kelly:

I am writing to you on behalf of Susan G. Komen (Komen) to express support for the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act and thank you for your leadership on this important issue. Komen believes that research to accelerate discovery and advance personalized care along with equitable access to affordable, high-quality breast health care for all patients are essential to reducing breast cancer deaths.

Breast cancer is the most common cancer diagnosed among women in the U.S. and is the second leading cause of cancer death among women after lung cancer. One in eight women in the U.S. will develop breast cancer over the course of her lifetime. With the increasing availability of mammography screening, earlier detection and improvements in breast cancer treatment, the overall breast cancer mortality rate among women in the U.S. declined by 41 percent over the last 30 years.[1] It is still expected that an estimated 290,560 people in the United States will be diagnosed with breast cancer and 43,780 will die from the disease in 2022 alone.

Research shows that despite recent scientific advancements, there are widespread racial health disparities in breast cancer. For example, Black women are, on average, 40 percent more likely to die of the disease as compared to white women.[2] Black women are also more likely than white women to be diagnosed with aggressive breast cancers, such as triple-negative breast cancer and inflammatory breast cancer, and are more likely to be diagnosed at a later stage. Breast cancer disparities also exist for other historically marginalized groups. Breast cancer is the most common cancer diagnosed and the leading cause of cancer death for Hispanic/Latina women.[3] Also, Hispanic and American Indian/Alaska Native women are more than 30 percent more likely to be diagnosed with advanced stage breast cancer compared with white women.[4]

We support the DEPICT Act because inequitable care and outcomes are tied to inequitable research, including clinical trials. The participants in many clinical trials do not reflect the eventual patient

[1] American Cancer Society. Breast Cancer Facts & Figures 2019-2020. (2019)
[2] Howlader N. SEER cancer statistics review (CSR) 1975–2016. National Cancer Institute. Available from: https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
[3] Power EJ. Breast Cancer Incidence and Risk Reduction in the Hispanic Population. Cureus. 2018;10(2):e2235. Published 2018 Feb 26. Doi:10.7759/cureus.2235
[4] AACR (2020).

communities that will utilize a therapy, which reduces access to the most novel therapies while they are under clinical review and leads to inequitable health outcomes once on the market. A recent study found that Black and Hispanic races were underrepresented with respect to their cancer incidence in clinical trials between 2008 and 2018 for FDA approved oncology drugs. Increased minority representation is required in trials to ensure the validity of results and reliable benefits to all.[5] For example, comorbidities that are more prevalent among Black and Hispanic women undergoing treatment, such as hypertension, diabetes and high cholesterol, place them at risk of severe, life-threatening side effects when given standard forms of chemotherapy, which may not be perceived in clinical trials that were conducted on white, more affluent populations.

Additionally, we know that minority populations face significant barriers which hinder their inclusion in clinical trials. This includes not even being offered the opportunity to participate in the first place, limitations in clinical trial locations, and community perception and distrust of the government and medical providers. These populations also face systemic barriers including lack of diversity in the health care workforce, lack of geographic and financial access to health services, systemic racism in health care, and prohibitive exclusionary eligibility criteria. Addressing these flaws in our health care system—and by consequence making clinical trials more accessible—is critical to addressing health disparities.

Komen supports efforts to reduce barriers and increase equitable access to participation in clinical trials for all populations and the DEPICT Act has the potential to do just that. We applaud your commitment to addressing such a needed policy solution and stand ready to assist you in making it law. If you have any questions, or we may be of further assistance, please do not hesitate to reach out to Komen's Director of Federal Policy and Advocacy, Aracely Panameño, at apanameno@komen.org or (972) 701-2071.

Sincerely,

Molly L. Guthrie

Molly Guthrie
Senior Director, Public Policy & Advocacy
Susan G. Komen

[5] Loree JM, Anand S, Dasari A, et al. Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals From 2008 to 2018. *JAMA Oncol.* 2019;5(10):e191870. doi:10.1001/jamaoncol.2019.1870

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March 16, 2022

The Honorable Anna Eshoo
Chair Subcommittee on Health
House Energy and Commerce Committee
Washington, DC 20515

The Honorable Brett Guthrie
Ranking Member Subcommittee on Health
House Energy and Commerce Committee
Washington, DC 20515

Statement for the Record on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"

Dear Chair Eshoo and Ranking Member Guthrie:

The American Academy of Neurology (AAN), the world's largest association of neurologists representing 38,000 professionals, is strongly committed to improving the care and outcomes of persons with neurologic illness in a cost-effective manner. One in six people lives with a brain or nervous system condition, including Alzheimer's disease, Parkinson's disease, stroke, epilepsy, traumatic brain injury, ALS, multiple sclerosis, and headache.

The AAN thanks the Energy and Commerce Subcommittee on Health for hosting the upcoming legislative hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight." Innovation in medicine is imperative, and we appreciate the Subcommittee's willingness to review key legislation that addresses this issue. More specifically, the AAN has endorsed H.R. 3085, the ENACT Act, and several key provisions included in H.R. 6000, the Cures 2.0 Act.

The ENACT Act: The Importance of Diversity in Clinical Trials

The AAN is committed to intentional action to be a fully inclusive, deliberately diverse, and anti-racist organization that respects and values our membership, our staff, and the communities we serve. We actively promote equity and social justice in neurology and the neurosciences. One action that can be taken to improve health care equity is making a deliberate effort to foster the inclusion of diversity in clinical trials. The AAN applauds the Subcommittee for including HR. 3085, the Equity in Neuroscience and Alzheimer's Clinical Trials (ENACT) Act to address the disparities in clinical trials. The ENACT Act would increase the participation of underrepresented populations in dementia clinical trials by expanding education and outreach, encouraging the diversity of clinical trial staff, and reducing participation burden, among other priorities.

Older Black and Latinx Americans are much more likely than White Americans to be affected by Alzheimer's and other dementias, yet many clinical research

studies focused on these diseases do not include sufficient data from these populations to be representative of the US population. The underrepresentation of these populations, along with Native American and Asian Americans, hampers our understanding about these health disparities and limits our knowledge of how potential therapeutics may affects populations that need them the most. This legislation aims to improve health care equity by taking deliberate actions to foster the inclusion of diversity in clinical trials. The ENACT Act would increase participation of underrepresented populations in dementia clinical trials by expanding education and outreach to these populations, encouraging the diversity of clinical trial staff, and reducing participation burden.

Cures 2.0 Key Provisions

Establishment of two additional Intercenter Institutes – Neurology Center of Excellence at FDA

The AAN supports Cures 2.0's efforts to establish two intercenter institutes at the Food and Drug Administration (FDA). Establishing the Neuroscience Center of Excellence at FDA has been a bipartisan, bicameral priority, and the AAN appreciates the leadership of Reps. DeGette and Upton on the H.R. 6000, the Cures 2.0 Act; Reps. Blumenauer, Pascrell, and Bacon on H.R. 5435, the BRAIN Act; and Senators Collins and Luján S. 3427, the Neuroscience Center of Excellence Act. Overall, the AAN supports the efforts of establishing an NCOE that is included in these bills. Despite the large societal need, medical products for neurological and psychiatric diseases and disorders are approved by the FDA at a much lower rate than products for other disease areas. We believe the creation of this center will enable several important goals, including placing a stronger emphasis on drug and device development tools for treatment and cures for psychiatric and neurologic diseases; increasing utilization of patient-focused drug and device development for people with psychiatric and neurologic diseases; and improving engagement between FDA and stakeholders and strengthening internal coordination within FDA.

The Creation of APRA-H

The AAN supports the authorization of an Advanced Research Projects Agency– Health (ARPA-H) that has been recently funded by the omnibus package. The omnibus provides $1 billion to establish the ARPA-H within the HHS. As highlighted by the administration, ARPA-H would have the potential to fund high-risk, high-reward research, such as new approaches to accelerate discovery of brain imaging and blood biomarkers. APRA-H could help contribute to the rapidly growing need to better understand the brain and nervous system. The omnibus legislation authorizes the President to appoint an ARPA-H director and allows the Secretary to transfer ARPA-H to any HHS agency or office, including the NIH, within 30 days of the omnibus's enactment.

While the funding has been secured, in addition to using DARPA as a model for ARPA-H, the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative could also be a useful example in promoting collaboration and transformational discoveries. The BRAIN Initiative is a unique public-private partnership that involves the NIH, DARPA, the National Science Foundation (NSF), the FDA, the Intelligence Advanced Research Projects Activity (IARPA), and private organizations. One program funded by IARPA, the Machine Intelligence form Cortical Networks (MICrONS), uses a nimble, contract-driven approach to map the function and connectivity of cortical circuits to advance use of machine learning algorithms. IARPA collaborates with other BRAIN Initiative partners to share brain imaging data that can help inform additional neuroscience research. Many of these BRAIN Initiative projects focus on technologies and data analytics that could serve as a model for ARPA-H efforts. Given the existing success of the BRAIN Initiative and other innovative entities including NCATS and BARDA, ARPA-H should also have a clear scope of work to ensure synergy without redundancy.

Understanding the Implication of Long Covid

The AAN remains dedicated to reviewing research concerning the impact of Long Covid on patients. Since 2020, our knowledge of COVID-19 has significantly grown. With science at the forefront of policymaking, synthesizing research to formulate the best path forward is imperative. According to a recent study, one-third of patients diagnosed with COVID-19 developed psychiatric or neurologic disorders within six months, including depression, anxiety, stroke, and dementia. In that same study, researchers who evaluated more than 230,000 electronic health records, which includes anonymous data from 81 million patients, primarily in the US, found that among COVID-19 patients admitted to an intensive care unit (ICU), the incidence of developing a psychiatric or neurologic disorder rose to an unprecedented 46 percent. If left unchecked, post-acute sequelae of SARS-CoV-2 infection (PASC) could leave many unable to perform their jobs, severely impacting the workforce, and increasing costs of health care.

Given the number of COVID-19 cases across the US, the impact of neurologic symptoms is likely enormous, and without proper information sharing, patients could suffer devasting consequences and misdiagnoses. Additionally, understanding the core causes of PASC will make it easier for providers to identify patients who are more at risk of developing its chronic symptoms, and potentially taking measures to prevent them.

Mitigating COVID-19's Impact on Basic Research

The AAN also applauds the inclusion of the bipartisan, bicameral RISE Act (H.R. 869/ S. 289) in the Cures 2.0 legislation, which we believe would provide crucial funding to support NIH-funded research—to continue federally-funded research that has been stalled, delayed, or was even stopped as a result of the pandemic. The long-term consequences of the COVID-19 pandemic on the country's biomedical research enterprise are becoming clear: funds are being diverted to support COVID-19-related research to the detriment of research on conditions within the missions of NIH's 27 institutes and centers and the new COVID-19-related expenses incurred to run research reduced the buying power of existing grants. This provision authorizes $25 billion in funding for grants from multiple agencies to support scientific researchers and institutions, covering the costs of research disruptions related to the COVID-19 pandemic.

FDA Cell and Gene Therapy

With many gene therapies on the horizon with the potential to treat neurologic disease, the AAN supports the directive to submit a report on the current state of cell and gene therapy regulation. The first commercial gene therapy targeted to treat a neurologic disease, onasemnogene abeparvovec-xioi (Zolgensma), has revolutionized treatment options for children with spinal muscular atrophy, a previously untreatable and fatal neurologic disorder of childhood. However, insurance coverage of this life changing therapeutic remains a challenge due to its $2.1 million price tag. The report will also provide an opportunity to better evaluate current initiatives, including the National Institute of Neurological Disorders and Stroke's Ultra-rare Gene-based Therapy (URGenT) network. This new program will support the development of gene-based therapies for ultra-rare neurologic diseases.

The Inclusion of the Telehealth Modernization Act

The AAN has long supported the telehealth provisions included in the Cures 2.0 Act. Telehealth is essential to ensure that patients are able to maintain a stable relationship with their physician after the completion of the COVID-19 related public health emergency (PHE) declaration, regardless of their personal circumstances. The temporary extension of telehealth flexibilities after the end of the PHE provided in the recent omnibus legislation will provide more time for legislators and industry representatives to meet and solidify a long-term plan for telehealth coverage. Overall, we believe a

long-term solution is the Telehealth Modernization Act, which is included in the Cures 2.0 Act. It is imperative that telehealth services are accessible to all patients and that there are no restrictions on patient location or for conditions that are appropriate to be treated and monitored remotely. The patient's home is a critical originating site for many patients, but it can be inadequate for those without access to broadband, appropriate technology, or the space to have a private conversation with a health care provider. Maintaining telehealth coverage is essential to protecting Medicare's most vulnerable patients, as well as reducing health care disparities.

The COVID-19 PHE has made clear that providing access to care via telehealth is valuable in all communities, not solely rural areas, or communities with a shortage of health professionals. We thank the Subcommittee for its support on the permanent elimination of the statutory restrictions on Medicare telehealth care delivery based on geographic location. This change would benefit patients and providers and is a positive step towards removing limitations to health care access when telehealth is clinically appropriate. The AAN also supports the requirement that GAO report on recommendations to enhance Medicare coverage and reimbursement for innovative health technologies to better address the needs in the future.

In conclusion, we thank you for hosting this legislative hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight." If you have any questions or require additional information, please do not hesitate to contact Derek Brandt, Director of Congressional Affairs at *dbrandt@aan.com* or Fred Essis, Congressional Affairs Manager at *fessis@aan.com*. We look forward to working with you as we all strive to improve care for all Americans with neurologic conditions.

Orly Avitzur, MD, MBA, FAAN
President, American Academy of Neurology

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

March 17, 2022

The Honorable Anna Eshoo
Chairwoman, House Energy & Commerce Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Brett Guthrie
Ranking Member, House Energy & Commerce Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

RE: House Energy and Commerce Subcommittee on Health Hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

Dear Chairwoman Eshoo, Ranking Member Guthrie, and Members of the Subcommittee,

The Association of Clinical Research Organizations (ACRO) appreciates the opportunity to submit this statement for the record for the Subcommittee's hearing, "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

ACRO represents the world's leading clinical research and technology organizations. ACRO and its members advocate on a global basis for safe, ethical, high-quality medical research so that patients can benefit from the timely development of new treatments and therapies. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices—from pre-clinical, proof of concept, and first-in-man studies through post-approval and pharmacovigilance research. With more than 200,000 employees engaged in research activities in 114 countries, ACRO member companies manage or otherwise support a majority of all FDA-regulated clinical investigations worldwide.

The COVID-19 pandemic presented a significant challenge to the clinical research industry, but thanks in large part to the work ACRO member companies have been doing for the past 20 years as part of the Association—and through valued partnerships with policymakers, regulators, and other stakeholders—ACRO members were able to meet the challenge head on and help to develop multiple vaccines in record time.

ACRO appreciates all the hard work the Subcommittee has done in preparation for today's hearing. ACRO and its members have spent the better part of the past two years focused on advancing diversity and inclusion in clinical research and advancing the adoption of decentralized clinical trials (DCTs)—two issues we are pleased to see be included in many of the bills being considered in today's hearing.

Improving Diversity and Inclusion in Clinical Research

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

ACRO is extremely supportive of the work Congress is doing to bolster diversity and inclusion in clinical research, not only among participants but throughout the research workforce. ACRO and its members are focused on a multitude of issues to be addressed to make our vision of a truly representative clinical research ecosystem a reality. We need to ensure that we are supporting robust clinical trial networks and that research is being conducted in the communities of the patients we're hoping to reach. We need to improve awareness and access so that historically excluded populations know that clinical research opportunities are available to them. We must solve issues regarding data completeness and granularity to be confident that we are enrolling the right trials into the right patients. Additionally, we will need to tackle global harmonization efforts so that trials are able to run smoothly around the world.

ACRO's Committee on Diversity & Inclusion in Clinical Trials has developed a Statement of Principles to guide the work our members do to make meaningful improvements in the representativeness of clinical trials. The statement includes the following four pillars:

- Improving Health Equity Through Access to Trials
    - Increase awareness and opportunities for clinical trial participation among diverse populations
    - Reduce the burden of participation for diverse communities through innovative methodologies, decentralized trial support services, and digital technologies
    - Work with predominantly underrepresented communities to build trust between stakeholders
- Empowering Research Partners (Patients, Sites, Health Care Providers)
    - Educate and engage patients as research partners throughout the clinical development lifecycle
    - Harness data to better characterize relevant patient populations
    - Support sites with training and culturally relevant materials to work with diverse communities
    - Use data to identify investigators with access to clinically relevant, diverse patients
- Partnering with Stakeholders & Policymakers
    - Work with policymakers and regulators around the world to promote policies that improve diversity and inclusion of underrepresented study participants
    - Embed a patient-centric mindset in policy recommendations by partnering with patient and minority advocacy groups
    - Collaborate with other industry groups to drive progress towards inclusive clinical trials
- Driving Workforce Diversity, Equity, & Inclusion
    - Support programs that drive diversity and inclusion in the clinical research industry workforce including employee retention, recruitment, and development

- Foster relationships with minority healthcare associations and other groups to bring new generations into clinical research

ACRO sees the meaningful work of improving diversity and inclusion in clinical research as a collaborative effort that requires participation from a broad group of stakeholders. We encourage Congress to continue its important work on this front, especially through many of the bills up for consideration today, and to ensure the inclusion of these groups—clinical research organizations, technology providers, sponsors, sites, patients, etc.—in diversity and inclusion initiatives going forward.

Driving the Adoption of Decentralized Clinical Trials

ACRO appreciates Congress' focus on improving adoption of decentralized clinical trials (DCTs). The ability to decentralize pieces of the clinical research process, to really bring the trial to the patient, is a tremendous step forward in the modernization of clinical research. These decentralized elements will allow us to reach more patients than ever before and aid in our goal of improving diversity and inclusion, not just racial diversity but geographical as well. We should be mindful not to assume that DCTs are a quick fix to struggles regarding inclusion, as will may face hurdles such as access to and understanding of technology, but it is certainly a step in the right direction. To make this adoption possible it is important that we gain clarity from regulators around the acceptance of these DCT elements so that clinical trial sponsors can have confidence including them in protocols going forward.

ACRO's Decentralized Clinical Trials Working Party was formed in 2019 to examine the barriers to adoption of DCTs and create quality-based principles and tools to facilitate implementation of DCTs. With the onset of the COVID-19 pandemic in 2020, the work of ACRO's DCT Working Party became even more important to ensuring that trials continued to run, and that patients and regulators could have confidence in both the safety and data integrity of clinical research through the pandemic.

As part of the DCT Working Party's work, the team developed a series of Data Flow Maps to build confidence and trust in DCTs by providing transparency and visibility into data flow, data controls, and data traceability with a DCT to illustrate how a decentralized model guards data quality and integrity. The Data Flow Maps address eConsent, Direct-to-Patient Shipping, Investigator-Participant Interactions, Connected Devices, and Home Health Visits.[1] Below you will see the Connected Devices Data Flow Map that outlines how data collected from wearable devices moves through the trial.

[1] All of ACRO's DCT resources can be found here.

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

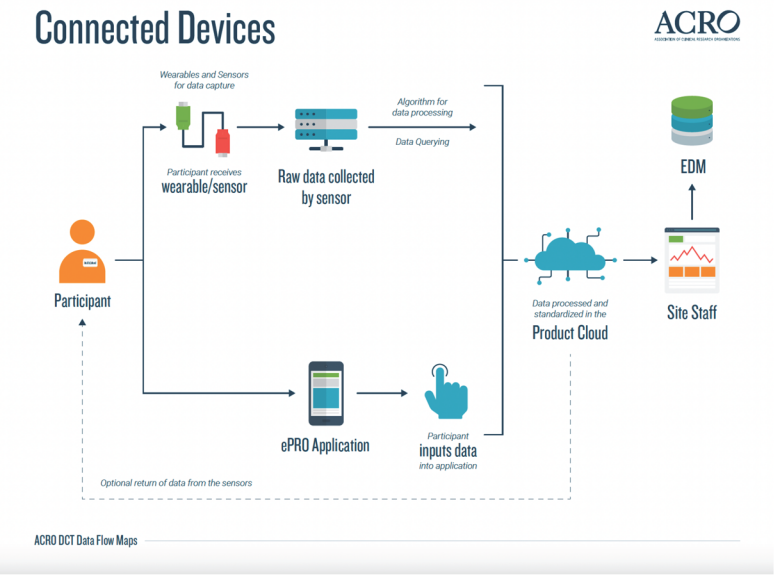

Figure 1. Connected Devices data flow map as developed by ACRO's Decentralized Clinical Trials Working Party. Participant enrolls into trial and receives connected devices in the form of the wearables/sensors for data capture and/or the electronic patient reported outcomes (ePRO) application (on a personal or provisional device). Raw data collected by the wearables/sensors are queried using the algorithm for data processing, and later the data are processed and standardized in the product cloud. The data input by the participant into ePRO is also processed and standardized in the product cloud. From here, the data on ePRO inputs and wearables/sensors are directed to site staff, and later into the electronic data management (EDM) system.

Conclusion

ACRO would like to thank the Subcommittee for the opportunity to provide this statement for the record for this important hearing. We appreciate your leadership and look forward to working with you further on these issues.

Sincerely,

Sophia McLeod
Director of Government Relations
smcleod@acrohealth.org

March 16, 2022

The Honorable Patty Murray
United States Senate
Committee on Health, Education, Labor and Pensions
428 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Richard Burr
United States Senate
Committee on Health, Education, Labor and Pensions
428 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Frank Pallone
United States House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
United States House of Representatives
Committee on Energy and Commerce
2322 Rayburn House Office Building
Washington, DC 20515

Dear Chair Murray, Ranking Member Burr, Chairman Pallone, and Ranking Member McMorris Rodgers:

We, the undersigned pediatric cancer advocacy organizations, write to express our strong support for the **Give Kids a Chance Act, HR 6972**. This bipartisan legislation seeks to ensure that combinations of oncology therapies will be studied in children's cancer, a critical step in ensuring that clinical research maximizes the chance of producing cures for children with currently untreatable cancers.

The Give Kids a Chance Act is an expansion of the RACE for Children Act and the Pediatric Research Equity Act (PREA). In 2003, Congress passed PREA, authorizing FDA to direct companies applying for FDA approval for investigational therapies for adult diseases to also study their novel therapies in children with the same disease. In 2017, Congress extended PREA obligations to cancer therapies through the RACE for Children Act, empowering the FDA to direct companies to undertake pediatric studies of novel cancer therapies whose molecular targets were substantially relevant in pediatric cancers.

However, the RACE for Children Act only authorized FDA to require companies to study novel therapies as single drugs. Though there are many new and exciting cancer therapies being developed today, no one new drug is likely to be successful alone in addressing life-threatening cancers, including pediatric cancers. Effective combinations of drugs give patients with cancer the best chance of a durable response or cure. The Give Kid a Chance Act would correct this gap by empowering FDA to require companies to undertake pediatric studies of combinations of cancer drugs when the molecular targets of the therapies are also relevant in children's cancers. In addition, the Give Kids a Chance Act would enable the FDA to direct preclinical studies to establish the substantial relevance of the molecular targets of such therapies to children's cancers.

Without the Give Kids a Chance Act's passage, we will continue to face often insurmountable challenges to access the necessary drugs to undertake studies of combination therapies. We will continue run out of options for the children with the most deadly cancers even as combination trials are demonstrating promising results for adult cancers.

The Give Kids a Chance Act makes it possible for combinations of oncology drugs to be studied in children with cancer. We urge the passage of the Give Kids a Chance Act to create the opportunity for us to discover new combination treatments that might give these kids a durable response and even possibly a cure. If you have any questions, please do not hesitate to contact any of the undersigned hospitals directly.

Sincerely,

3/32 Foundation
Aiden Farr
Aiden's Army
Alex's Army Childhood Cancer Foundation
Angels for Change
Arms Wide Open Childhood Cancer Foundation
Avahstrong
Bear Necessities Pediatric Cancer Foundation
Beat Childhood Cancer Foundation
Brantley Francis Foundation
Brent's Place
Brooke's Blossoming Hope for Childhood Cancer Foundation
Caleb's Crusade Against Childhood Cancer
Canceragogo
Caring with Grace
Carmella Strong
Carpe Diem Coaching
Carson Leslie Foundation
ChadTough Defeat DIPG Foundation
Children's Hospital Colorado
Christina Renna Foundation Inc.
Clinton County Progressives
Curing Kids Cancer
Curiosity Shots
DADA2 Foundation
DanceBlue Kentucky Children's Hospital Hematology / Oncology
Dragon Master Foundation

Elaine Roberts Foundation
End Kids Cancer
Gabriella's Smile Foundation
Gold In September
Gold Rush Cure Foundation
Grandparents In Action
Handstand Walk for Kids
Handstand walk with Eloise
Hannah's Cans For Cancer
Hunter's Cancer Journey
Joey's Wings Foundation
JR Schoen Memorial Foundation, Inc.
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Kick Childhood Cancer Guild
Kids V Cancer
Love Smiles
Lymphedema Advocacy Group
Mackey Family Childrens Cancer Foundation
Making Headway Foundation
Matthew's Hope 4 Miracles
Maynard Childhood Cancer Foundation
McKenna Claire Foundation
Musella Foundation For Brain Tumor Research & Information, Inc
Mystic Force Foundation
Northwest Indiana Cancer Kids Foundation
Our Amazing Fighters
Pediatric Assessment, Learning & Support
Pediatric Brain Tumor Foundation
Pediatric Cancer Foundation
Phoenix Stone Foundation
Press On Fund
Rally for Ally
Rally Foundation for Childhood Cancer Research
Rett's Roost
Robby Butler Superhero Fund
Roe Roe's Heroes Childhood Cancer Foundation
Sadie Keller Foundation
Solving Kids' Cancer
Swifty Foundation
Team G Childhood Cancer Foundatio

Teen Cancer America
The Alan B. Slifka Foundation
The Catherine Elizabeth Blair Memorial Foundation
The Cure Starts Now Foundation
The Gold Hope Project
The Kortney Rose Foundation
The Lilabean Foundation for Pediatric Brain Cancer Research
The Maeve McNicholas Memorial Foundation
The Max Cure Foundation
The Scott Carter Foundation
The Taylor Matthews Foundation
The Valerie Fund
Tough2gether Against DIPG
Unravel Iowa
Unravel Pediatric Cancer
Until 20, LLC
West Virginia Kids Cancer Crusaders
William's Warriors
Wyatt's Warriors
Wylie's Day Foundation

Statement for the Record
House Committee on Energy and Commerce Hearing:
"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
March 17, 2022

The Honorable Frank Pallone
Chair
House Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
Ranking Member
House Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

Dear Chairman Pallone, Ranking Member McMorris Rodgers, and Members of the Committee:

Arnold Ventures appreciates the opportunity to submit this statement for the record for the committee's hearing, "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

Arnold Ventures is a philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice. Our work within the health care sector is driven by a recognition that the system costs too much and fails to adequately care for the people it seeks to serve. We prioritize five objectives to make health care more affordable and accessible: lower prescription drug prices; lower excessive commercial sector prices charged by providers; improve provider payment to incentivize the delivery of high-quality and efficient care; ensure Medicare's financial sustainability; and improve care for people with complex care needs.

Our work on prescription drugs focuses on the drivers of high drug and biologic prices and spending: patent abuses and anti-competitive behaviors; market distortions; and high launch prices and unjustified price increases. Our work also focuses on ensuring that the U.S. Food and Drug Administration (FDA) drug and biologic approval process incentivizes innovation by using clinically meaningful evidence that is based on patient outcomes, and requiring that trial data be publicly available and comparable across products.

To that end, we appreciate the committee's efforts to support and strengthen the critical work of the FDA, and we support continued efforts to implement policies that strike a balance between promoting innovation, creating access, and ensuring the safety and efficacy of drugs on the market.

A key piece of the FDA's efforts to bring more therapies to patients faster has been the Accelerated Approval Program. The FDA established the program 30 years ago to speed the approval of drugs and biologics that treat serious conditions and fill an unmet need by permitting clinical trials to use surrogate endpoints and requiring confirmatory clinical evidence to be collected at a later date. Some drugs and biologics approved through the accelerated approval pathway will have strong, direct patient benefits on survival, symptoms and/or patient function, as

is true with drugs used to treat HIV/AIDS.[i] Others, however, have no direct clinical benefit and pose considerable risk to patients after years of market access.

The FDA approval of the Alzheimer's disease drug aducanumab is an excellent example of why reforms to the Accelerated Approval Program are warranted. The FDA approved aducanumab despite evidence of severe clinical harms such as brain swelling and bleeding, and without clear evidence of clinical improvements in patient cognition.[ii] Further, an FDA advisory committee overwhelmingly rejected the premise that the data collected in clinical trials using a surrogate endpoint of amyloid reduction on brain scans could be extrapolated to drug effectiveness in slowing cognitive decline.[iii]

As the Accelerated Approval Program exists today, we note three areas of concern:

1. The growing use of surrogate endpoints that are divorced from direct patient outcomes (e.g., survival, gain of function, symptom abatement).
2. The lack of timely completion of confirmatory trials.
3. Inadequate efforts to withdraw from the market products that fail confirmatory trials.

Additionally, manufacturers are charging high prices for new drugs approved through the accelerated approval pathway before direct patient benefits are confirmed. Biogen, for example, is charging about $28,000 per year for aducanumab.[iv] Paying for medications with questionable efficacy and, in the case of aducanumab documented harms, uses taxpayer dollars that could otherwise be directed toward higher value services.

As is true for the majority of expedited or amended approval pathway programs used by the FDA, the percentage of drugs approved under the Accelerated Approval Program has increased over time.[v] From 1992 - 2020, FDA issued more than 250 accelerated approvals, most for oncology drugs.[vi] Some drugs or biologics are exclusively marketed for indications approved under the accelerated approval pathway, while others have several approved indications for which the accelerated approval pathway is used for a subset.

As required by law and regulation, sponsors of drugs that use the accelerated approval pathway must verify and describe the clinical benefit of the surrogate endpoint through adequate and well-controlled confirmatory trials.[vii] However, post-approval confirmatory trials are often delayed and many have been found to use the same incompletely validated surrogate endpoints from the preapproval trials.[viii,ix] As shown over time, some surrogate endpoints can be poor predictors of the effects of drugs on patient health outcomes.[x] As of July 2021, of the 18 accelerated approval indications with negative post-approval trials (those that did not confirm a clinical benefit), six remained on formal FDA approved drug labelling and continued to be recommended in clinical guidelines.[xi]

In 2019, Medicare spent $9.1 billion (Part D: $3.2 billion; Part B: $5.9 billion) on drugs with at least 1 indication that was approved using the accelerated approval pathway.[xii] From 2015 – 2020, Medicaid spent $6.7 billion on drugs with accelerated approval, of which 33 percent were on drugs exclusively marketed for indications approved under the accelerated approval pathway, and 31 percent on drugs approved under the accelerated approval pathway that, after at least five years, have yet to complete the confirmatory trial.[xiii] During this time period, total Medicaid net spending on drugs with at least 1 accelerated approval indication doubled.

It is clear that through the incentives of the Accelerated Approval Program, needed therapies have been brought to patients faster. We believe that Congress should improve guardrails to ensure that drugs coming to market under this pathway meet the same stringent safety and efficacy standards as any other product approved by the FDA. Congress can also consider adjustments to Medicare and Medicaid payment policies to incentivize manufacturers to complete confirmatory trials in a timely manner to ensure that payers, providers, and patients can trust the value of these therapies over existing standards of care.

We appreciate the committee's commitment to improving the Accelerated Approval Program. Please reach out to Mark Miller (mmiller@arnoldventures.org) or Andrea Noda (anoda@arnoldventures.org) with any questions.

Sincerely,

Andrea Noda
Vice President, Health Care
Arnold Ventures

[i] https://www.fda.gov/media/86284/download
[ii] https://www.nytimes.com/2021/11/22/health/aduhelm-death-safety.html
[iii] https://www.fda.gov/media/145690/download
[iv] https://www.fiercepharma.com/pharma/biogen-halves-aduhelm-price-layoffs-ahead-medicare-decision-controversial-alzheimer-s-drug
[v] https://jamanetwork.com/journals/jama/article-abstract/2758605
[vi] https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals
[vii] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.500
[viii] https://www.healthaffairs.org/servlet/linkout?suffix=B6&dbid=16&doi=10.1377%2Fhlthaff.2021.00762&key=10.1001%2Fjamainternmed.2019.0462
[ix] https://www.healthaffairs.org/servlet/linkout?suffix=B7&dbid=16&doi=10.1377%2Fhlthaff.2021.00762&key=10.1001%2Fjama.2017.9415
[x] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2764287
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[xii] https://jamanetwork.com/journals/jama-health-forum/articlepdf/2786897/rome_2021_ld_210024_1638463484.49075.pdf
[xiii] https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2021.00762?journalCode=hlthaff

Howard "Skip" Burris, MD, FASCO
President, Association for Clinical Oncology

Comments prepared for the
U.S. Senate Committee on Health Education Labor & Pensions
and
U.S. House Energy & Commerce Committee

On the Food and Drug Administration Reauthorization Act of 2022 (FDARA)

March 17, 2022

The Association for Clinical Oncology (ASCO) is pleased to have the opportunity to offer comments on the *Food and Drug Administration Reauthorization Act of 2022* (FDARA), the legislation to reauthorize the Food and Drug Administration's (FDA) industry user fee authorizations (UFA). We appreciate the significance of the FDARA and have compiled the list below of ASCO policies that we hope you consider in addition to the reauthorization of the UFAs as the debate of the FDARA continues.

ASCO is the world's leading professional society representing physicians who care for people with cancer. With nearly 45,000 members, our core mission is to ensure that cancer patients have meaningful access to high quality cancer care.

We applaud your commitment to moving FDARA in a timely manner to continue this progress and prevent any disruption in the approval of safe and effective therapies for patients by the FDA.

Increasing Diversity in and Access to Clinical Trials

As cancer care becomes more complex and personalized, the research through which new advances are developed must include diverse representation of participants. ASCO believes that all populations should have an equal opportunity to participate in, be recognized for, and benefit from research across the spectrum, including clinical trials. However, due to a variety of barriers, many patient populations continue to be underrepresented in clinical trials and health care-related research.

ASCO has long supported policies that would increase access to clinical trials to historically underrepresented populations. The *21st Century Cures 2.0* (H.R. 6000) legislation introduced last year contains several provisions that would foster inclusion in biomedical research trials. ASCO responded to the legislation, supporting specific provisions that would require: an update from the FDA on efforts to improve diversity in trials, a GAO study on barriers to clinical trial participation, a public awareness campaign by the Department of Health and Human Services (HHS) to increase awareness and understanding, particularly in minority communities, of clinical trials and a task force on making clinicaltrials.gov more user- and patient-friendly.

In addition to the provisions in *Cures 2.0,* ASCO strongly supports passage of the *Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Trials Act* (H.R. 5030/S. 2706) and urge you to prioritize this bill for enactment into law this year. The *DIVERSE Trials Act* would make it easier for all patients to participate in clinical trials while removing barriers that are known to keep certain racial and ethnic groups, older adults, rural residents, and those with limited incomes from being appropriately represented.

The three provisions of the *DIVERSE Trials Act* will result in more efficient, inclusive, and accessible research, which will benefit the health of all Americans. First, the legislation would permit individuals to receive financial support for the non-medical costs associated with their participation in clinical trials, by creating a statutory safe harbor for clinical trial sponsors to use in reimbursing such costs. Second, the bill would allow trial sponsors to provide individuals with the technology necessary for them to participate remotely in clinical trials. This commonsense approach addresses the issue that clinical trial participants almost always need to report their condition, symptoms, side effects, or other data on a regular basis and/or to have certain health indicators monitored by web-enabled technology. Finally, the legislation would require the Department of HHS to issue guidance on decentralized clinical trials. While the COVID-19 pandemic accelerated the need for patients to have clinical trials available to them at or close to home, researchers have long endeavored to make clinical trials more convenient in order to attract participants. The decentralized approach could open the door to clinical trials for a much broader array of participants, such as those who live hours from a trial site or do not have the ability to make repeated visits to the trial site due to work or caregiving schedules.

ASCO has also endorsed the *Diverse and Equitable Participation in Clinical Trials (DEPICT) Act,* legislation aimed at boosting diversity in clinical trials by requiring enhanced data reporting on clinical trial demographics and providing resources to improve access to clinical trials. Specifically, the bill requires Investigational New Drug (IND) and Investigational Device Exemption (IDE) applicants to report clinical trial enrollment targets by demographic subgroup, including age, race, ethnicity, and sex, and provide a rationale for those targets in addition to providing a Diversity Action Plan detailing the actions the sponsor will take, such as outreach and engagement strategies, to reach these enrollment targets. Additionally, the legislation would provide the FDA with the authority to mandate post-market studies when sponsors fail to meet diversity enrollment targets and do not provide a sufficient justification, and finally requires FDA to publish an annual report aggregating and analyzing the data provided by sponsors on their progress toward and strategies for improving diversity in clinical trials.

ASCO also appreciates the regulatory changes and flexibilities the Administration has allowed within federal agencies, particularly the FDA, the National Institutes of Health (NIH), and the National Cancer Institute (NCI) during the COVID-19 pandemic. The pandemic necessitated changes in clinical trial operations to mitigate disruptions in both care and research. Several of these changes proved successful and have now led to establishment of less cumbersome processes for patients and researchers. We believe there is an opportunity to learn from and build upon these design changes.

The agencies stepped in quickly to provide flexibilities that helped sites to safely maintain participants' access to study therapies, scans, and laboratory assessments – particularly allowing use of telehealth and remote clinics, scans, and labs. ASCO has urged extension of those flexibilities so trial participants can continue to access these patient-centered options even after the pandemic ends. As noted above, we support increasing patient access to clinical trials through models such as decentralization of trials and electronic consent to ensure required signatures and remote recruiting. COVID-19 caused trial

modifications such as remote assessments to be successfully deployed in the middle of large ongoing cancer trials. As mentioned, decentralized trials have the potential to reduce patient and sponsor burden and increase accrual and retention of a more diverse trial population, while at the same time reducing exposure to COVID-19 for vulnerable patient populations. ASCO is eager to work with Congress and the Administration to increase the use of decentralized clinical trial designs.

ASCO has also published a statement devoted to making clinical trials more representative by refining eligibility criteria. It is vitally important that patient access to clinical trials be broadened with the use of science-based, clinically relevant eligibility criteria. ASCO continues to work with the FDA and other stakeholders to implement these recommendations.

Expanding Access to and the Use of Real-World Evidence

Advances in health information technologies and a dramatic increase in the adoption of electronic health records (EHRs) have created new opportunities for streamlining clinical evidence through collection of real-world data (RWD). Data collection that captures demographic characteristics including race/ethnicity, sexual orientation, gender identity, socioeconomic status, age, stage of disease, comorbidities, etc. helps reduce health disparities by ensuring all patient populations are included in the development in treatments. Sources of RWD include electronic health records, insurance claims, patient registries, and digital health solutions outside of conventional clinical trials. Additionally, RWD has a largely untapped potential to supplement clinical trial data and improve external validity—and establish real-world effectiveness and toxicity, especially in oncology.

The *21st Century Cures Act* in 2016 tasked the FDA with implementing several provisions, including the Real-World Evidence (RWE) Program and Draft Guidance. This provision requires the FDA to publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions and requires the FDA to explore the use of RWE for additional indications of approved drugs and post-approved study requirements. Additionally, the FDA is working with the NCI on data sharing and data aggregation. These provisions will have implications for ASCO's clinical trial, the Targeted Agent and Profiling Utilization Registry (TAPUR), and data registry, CancerLinQ.

We appreciate this guidance beginning with acknowledging the important challenges involved in standardizing data derived from RWD sources. The lack of data standards presents a problem even beyond the contemplation of their use in the RWE regulatory framework. This is especially true in specialty fields such as oncology.

Several provisions within the *21st Century Cures 2.0* legislation would increase the ability to collect and utilize RWE. The bill would require drug manufacturers/sponsors to collect and report on patient experience data as part of the clinical trial; require the FDA to fully consider all patient experience data collected during the clinical trial; and require reporting of patient experience data in a transparent manner that is uniform, meaningful and informative to patients and providers. The bill would build on FDA's efforts by requiring HHS to outline approaches to maximize and expand the use of RWE; and establishing a task force to develop recommendations on ways to encourage patients to engage in real-world data generation. Additionally, *Cures 2.0* would require the HHS to submit a report to Congress on the efforts to ensure collaboration and alignment across the centers and offices of the FDA with respect to the regulation of digital health technologies

ASCO has also endorsed the *Meaningful Access to Federal Health Plan Claims Data Act* (H.R. 5394). This policy provides clinician-led clinical data registries with access to Medicare claims data for purposes of research to improve quality and cost efficiency by linking the data with clinical data in registries, a necessary step towards ensuring providers have access to the full spectrum of relevant data.

ASCO urges the Committees to prioritize these provisions to allow our healthcare continuum to continue building on the use of RWE and RWD as a way to reduce healthcare disparities.

Ensuring Patients Access to Life-Saving Therapies

ASCO has long supported the accelerated approval and complementary expedited review programs, which provide patients with the earliest possible access to potentially life-saving therapies, instead of requiring them to wait for confirmation of long-term endpoints, such as survival. Specifically, the Accelerated Approval Program allows for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint that demonstrates drug value and an improvement in patient outcomes. The benefit of the program is that life-saving drugs reach patients faster, however many worry that the earlier a treatment is available to patients, the less safety information exists about a particular drug and the harder it may be to complete the confirmatory trials when a patient can receive the drug by prescription.

To mitigate the risks, the FDA uses the same standards to approve treatments via accelerated approval as they would via a traditional pathway; drugs must demonstrate substantial evidence of safety and that the "drug is safe for use under conditions prescribed, recommended or suggested in the proposed labeling" and must meet the standard for effectiveness, which requires substantial evidence based on "adequate and well controlled clinical investigations." Sponsors must also agree to conduct a post-marketing confirmatory study or studies to verify and describe the relationship between the endpoint and the expected clinical benefit following a drugs approval via the accelerated approval pathway. Additionally, as part of its review, the FDA considers the overall risk and benefit of approving, rejecting, or waiting to approve the drug. This evaluation considers the risk for patients who lack access to effective treatments.

The Accelerated Approval Program has been vital for cancer treatment development. Between 2010 to 2020, 85% of accelerated approvals were for oncology indications. While survival is always the end-goal, there are many ways to evaluate benefit of a drug to the patient and their quality of life, including reduction of the size of the tumor, delay in the progression of the disease, and the establishment of complete response rates in hematological diseases. Our understanding of cancer and its treatment is changing every day. Our regulatory systems must adapt in ways that meet a rapidly evolving science, deliver cutting edge treatments to patients, and balance safety with risk.

Despite the relative success of the program, the FDA could benefit from additional tools and flexibilities to advance this pathway with the growing need to ensure the completion of confirmatory trials. Currently, there are two bills that would assist the FDA in improving its ability to utilize the accelerated approval pathway. The *Accelerated Approval Integrity Act* (H.R. 6963) and the *Accelerating Access for Patients Act* (H.R. 6996) would both provide FDA with additional authority to ensure products that receive accelerated approval are providing a clinical benefit to patients in a timely manner.

Reforming Federal Oversight of Laboratory Developed Tests

In August 2020, the Trump Administration issued an order barring FDA from requiring premarket review for any laboratory developed tests (LDTs) unless the agency goes through formal rulemaking procedures. This action has created considerable uncertainty for clinical laboratories creating diagnostic tests and the Biden Administration has not yet rescinded the order.

ASCO calls on Congress to work with stakeholders and the FDA to provide clear guidelines for the review and approval process of LDTs. Specifically, ASCO is supportive of the bipartisan *Verifying Accurate Leading-edge IVCT Development (VALID) Act* (H.R. 4128/S. 2209), which would create a distinct regulatory framework for in vitro diagnostics and LDTs, known collectively in the draft legislation as in vitro clinical tests (IVCTs).

The framework features a tiered, risk-based system for the regulation of IVCTs. As already happens with medical devices, FDA would typically subject high-risk IVCTs to a preapproval review but low-risk diagnostics would be able to come to market after listing with the agency. The framework features a middle tier of IVCTs that would need to obtain approval but without meeting the same requirements as high-risk diagnostics. Other provisions include the creation of a breakthrough designation.

We believe that reforming the regulatory framework for clinical laboratory diagnostics is essential to protect patients and ensure access to innovative and high-quality testing. The ongoing COVID-19 pandemic has only underscored the importance of reliable testing and reinforced the need for a uniform regulatory framework that consistently holds all clinical tests to the same risk-based standards.

However, the current system of oversight is inadequate, having failed to keep pace with changes in the testing industry and to match regulatory requirements with the risk that certain tests pose to public health. ASCO encourages these Committees to prioritize diagnostics reform, taking into consideration the significant work that has been done thus far in the development of the *VALID Act.* Though more must be done to ensure regulators have access to the information and tools needed to ensure that flawed tests do not reach vulnerable patients, the *VALID Act* represents the most comprehensive reform effort to date and reflects years of negotiation and compromise among industry and stakeholder groups.

Addressing Critical Manufacturing and Supply Chain Inadequacies

Over the last several years, natural disasters, quality problems, manufacturer consolidation, disruptions to raw ingredient supplies, and other emergencies that take place in countries which house critical drug manufacturing facilities have left the U.S. healthcare system on the brink of a significant public health crisis multiple times. The COVID-19 public health emergency further underscored the vulnerability of our nation's healthcare supply chain. During the pandemic, healthcare providers struggled to obtain medications and supplies essential to patient care, including the sedatives necessary to mechanically ventilate patients, personal protective equipment (PPE) such as gloves and masks, and ancillary devices and supplies, such as syringes and swabs. The pandemic stress-tested our supply chains, highlighting their fragilities and deficiencies, throwing the need for immediate corrective action into sharp relief.

The FDA is instrumental in helping to mitigate the effect of drug shortages. To help prevent and overcome drug shortages, the FDA uses tools such as expedited facility inspection, expedited new and/or generic drug applications, and the exercise of discretion with respect to the temporary importation of products from foreign manufacturing sources. The agency may also urge manufacturers

to increase production in specific situations to meet anticipated increases in demand. In response to the COVID-19 pandemic, Congress increased FDA authority to identify, prevent, and mitigate possible drug shortages by, among other things, enhancing FDA's visibility into drug supply chains. These authorities were included in the *Coronavirus Aid, Relief, and Economic Security (CARES) Act*. ASCO supported these measures, but as noted, more permanent authority is necessary to combat future shortages and disruptions to our supply chain.

We encourage Congress to take the following actions:

- Require manufacturers to be more transparent with the FDA about potential drug shortages
- Require manufacturer transparency around their sources of raw material (active pharmaceutical ingredients, API) including which state and country the API come from
- Require manufacturers of critical medications and supplies to develop a reasonable contingency plan in the event of a production interruption or shut down
- Create requirements for supply chain resiliency, including multiple manufacturing sites for important drugs and multiple suppliers of API for the same drug
- Create incentives for manufacturers to increase production when drug shortages occur

Specifically, ASCO has endorsed the *Pharmaceutical Accountability, Responsibility, and Transparency (PART) Act* and the *Help Onshore Manufacturing Efficiencies for Drugs and Devices (HOME) Act* – yet to be reintroduced in the 117th Congress. The *PART Act* would expand reporting requirements for manufacturers and require quarterly disclosures to the FDA on critical manufacturing data such as which medications and what in amount – including active pharmaceutical ingredients – are produced domestically and abroad. The *HOME Act* would help reduce U.S. reliance on foreign sources for critical drugs and medical supplies and ramp up American manufacturing capacity.

Both the *PART Act* and the *HOME Act* take important steps in solving the complex issues that create drug shortages in the United States and put safeguards in place to ensure that future shortages are limited. It is ASCO's hope that with the safety and transparency requirements offered in these bills, we will be one step closer to creating a strong, stable pharmaceutical manufacturing pipeline to ensure U.S. health care security and pharmaceutical access for all patients with cancer.

ASCO has also provided comments on the draft legislative package, the *Prepare for and Respond to Existing Viruses, Emerging New Threats, and Pandemics Act (PREVENT Pandemics Act*), supporting the important provisions included to strengthen the medical products supply chain and mitigate future drug shortages.

***

Thank you for the opportunity to provide these additional ideas as you work to renew the FDA industry user fee authorizations. We look forward to working further with you and your staff as this process moves forward. Please contact Kristin Stuart at Kristin.Stuart@asco.org with any questions.

Opinion

Lisa Jarvis

Congress Needs to Fix the FDA's 'Accelerated' Drug-Approval Process

The agency needs the authority to demand prompt clinical trials to demonstrate that medicines actually work.

The FDA needs to see that all drugs help patients. *Photographer: Stan Honda/AFP via Getty Images*

By Lisa Jarvis
March 16, 2022, 7:00 AM EDT

Congress is targeting a strategy that drug companies have increasingly used to speed up the approval of their medicines. Legislation in the House of Representatives would put more guardrails on the Food

and Drug Administration's so-called accelerated approval pathway.

The bill, from Representative Frank Pallone, a New Jersey Democrat, offers needed fixes for a system that can allow questionably effective – and often breathtakingly expensive – drugs to linger on the market for years.

Understanding this situation requires a bit of background. The FDA devised accelerated approval in 1992 in response to the AIDS crisis. Scientists at the time discovered that certain immune cell levels in patients were an excellent proxy for measuring HIV drugs' efficacy. And the agency saw this as a way to give patients quicker access to promising new drugs that appear to affect the course of a disease but have not yet been shown to treat or cure that disease. In 2012, Congress authorized broader use of "accelerated approval" as part of the FDA Safety and Innovation Act.

Pharmaceutical companies have been allowed to seek approval for their drugs based on evidence of "surrogate outcomes" – that is, changes that predict, rather than directly demonstrate, a clinical effect.

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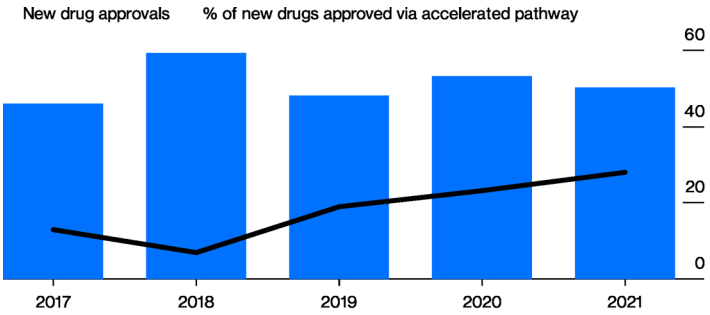
A cancer drug, for example, could be shown to shrink tumors rather than to prolong patient survival. A medicine designed to treat neurodegenerative disease might be shown to increase levels of a critical protein rather than to improve a patient's gait. The assumption is that, with further study, the demonstrated effects will prove to prolong survival or improve mobility – or in some way significantly benefit the patient.

The accelerated approval pathway has helped speed important new drugs to the market. And in the past five years, an increasing share of new drug approvals has relied on it. Last year, more than one in four new medicines – 28% – were given a green light based on surrogate outcomes.

Accelerated Approvals on the Rise

More new drugs are using a regulatory pathway that relies on proxy markers to indicate a clinical benefit



Source: FDA

But the process needs critical tweaks to ensure that studies are promptly done to show that those surrogate outcomes translate into real benefit for patients, without risk of dangerous side effects.

The FDA requires drugmakers to conduct such studies. However, companies have been slow to comply. Products remain on the market for many years – usually at great cost to patients and the health-care system – without strong evidence that they work.

Pallone's legislation would give the FDA greater power to hold drugmakers accountable for conducting the studies without delay.

The need for this fix became obvious last year, after Biogen was granted accelerated approval for its new Alzheimer's treatment, Aduhelm. Clinical trials of this drug had failed to show that it worked to slow cognitive decline. But the FDA approved it anyway – against the recommendation of its own committee of experts – based on a surrogate endpoint, its ability to clear away amyloid plaques from patients' brains.

The FDA gave Biogen an eye-popping nine years to complete a study (not unlike the ones the company had already run without good results) to show that amyloid reduction slows the course of the disease. And the company prepared to sell its new treatment for $56,000 a year. (After an uproar, it cut that price in half.)

Congress took note.

The proposed legislation would not have kept Aduhelm off the market. But it would make it harder for Biogen and other drugmakers to put off the hard work of proving their medicines actually work.

Pallone's bill would require drugmakers to start confirmatory trials as soon as the accelerated approval is granted, not years down the road. That means mapping out the study ahead of the approval. This is an entirely reasonable requirement, and it would allow companies to take advantage of existing clinical trial sites to start enrolling patients. Pallone wants to also require that the trial prove a clinical benefit, not merely rely on the same surrogate markers – a problem commonly seen in post-approval studies of cancer drugs.

Most important, pharma companies would face real consequences for not completing the post-approval studies. If they failed to confirm the drug's benefit within a year of the agreed-upon date (which would be no more than five years out), the approval would expire.

The legislation would also make it easier to take those drugs off the market. The FDA's existing process is clunky and time-consuming. And it's typically used only when a drug fails a post-approval study, not because the study wasn't completed.

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While waiting for Congress to provide greater authority, the FDA could also tighten the system somewhat on its own by being more selective about which drugs are allowed to use the accelerated approval pathway. In too many cases, surrogate endpoints take almost as long to measure as good old-fashioned efficacy; the FDA should allow their use only when they offer a meaningful shortcut to the market.

Congress should support Pallone's bill to give the FDA the muscle to ensure that all drugs on the U.S. market are safe and effective.

More from other writers at Bloomberg Opinion:

- Approving Biogen's Alzheimer's Drug Is a Big Mistake: Max Nisen
- The Big Question: Is the FDA's Drug Approval Process Broken?: Max Nisen
- The FDA Is Late in Banning E-Cigarettes That Tempt Kids: Michael R. Bloomberg

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March 17, 2022

The Honorable Patty Murray
United States Senate
Committee on Health, Education, Labor and Pensions
428 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Richard Burr
United States Senate
Committee on Health, Education, Labor and Pensions
428 Dirksen Senate Office Building
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The Honorable Frank Pallone
United States House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
United States House of Representatives
Committee on Energy and Commerce
2322 Rayburn House Office Building
Washington, DC 20515

Dear Chair Murray, Ranking Member Burr, Chairman Pallone, and Ranking Member McMorris Rodgers:

We write to strongly endorse the Give Kids a Chance Act, HR 6972 and to ask that Congress pass it into law.

We are the leading pediatric cancer clinical and preclinical consortiums. Almost all medical centers that treat children with cancer are members of one or more of us. Through our networks, children with cancer can access therapies the collective expertise of world-renowned pediatric specialists. We develop and coordinates cancer preclinical and clinical trials conducted at multiple institutions. We conduct studies of novel therapies as single agents and in combination in a variety of preclinical and clinical trial settings, supported by strong scientific rationales

The Give Kids a Chance would support our efforts to access and study combinations of novel targeted oncology therapies in children's cancers. Combinations of targeted cancer therapies often lead to the best chances of durable responses for the children with untreatable cancers. At this time, when there are hundreds of combination studies of targeted cancer agents in adult preclinical and clinical settings, we look forward to increasing our opportunities to study combinations in children's cancers

We urge Congress to pass the Give Kids a Chance Act.

Sincerely,

Children's Oncology Group (COG)
Pediatric Brain Tumor Consortium (PBTC)
New Approaches to Neuroblastoma Therapy (NANT)
Pacific Pediatric Neuro-Oncology Consortium (PNOC)
Pediatric Oncology Experimental Investigators' Consortium (POETIC)
Collaborative Network for Neuro-Oncology Clinical Trials (CONNECT)
Beat Childhood Cancer
DIPG Preclinical Consortium

Written Statement of Matthew Rizzo, MD, FAAN
Chair, American Brain Coalition
House Committee on Energy and Commerce
Subcommittee on Health
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight
March 17, 2022

Thank you for the opportunity to provide this statement for the record for the Subcommittee on Health's hearing on *The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight.*

I am the Frances & Edgar Reynolds Chair & Professor of the Department of Neurological Sciences; Co-Director of the Nebraska Neurosciences Alliance, and Director of Neurosciences Services at the University of Nebraska Medical Center. I am also honored to serve as the Chair of the American Brain Coalition (ABC). The ABC is a nonprofit organization comprised of the nation's leading professional neurological, psychological, and psychiatric associations and patient organizations. Together, the ABC seeks to advance the understanding the brain and reduce the burden of brain disorders for the millions of Americans who suffer from diseases affecting the brain and central nervous system (CNS). The ABC is reaching out today to urge the Committee to include provisions that will create a Neuroscience Center of Excellence at the Food and Drug Administration (FDA) within legislation that reauthorizes the prescription drug user fees.

Nearly one in five U.S. adults live with a mental illness. Neuropsychiatric disorders are also the leading cause of disability in the nation, making up 18.7% of years lost to disability and premature death.[1] Neurological conditions are troublingly prevalent as well - twenty million Americans suffer from a neurological condition, with 16% of households including an individual with a brain impairment.[2] Brain and CNS diseases also harm older Americans, with more than one in nine people over age 65 having Alzheimer's dementia.[3]

The enormous personal costs of brain and CNS conditions also translate to financial hardship for patients and their families and burden the U.S. economy. Brain disorders and diseases cost the U.S. more than $1.5 trillion per year,[4] a significant portion of which is borne by the Medicare program. Seven of the twenty-one chronic conditions tracked by the Centers for Medicare and Medicaid Services are related to the brain, representing an average annual cost of $23,325 per Medicare beneficiary – higher than the average cost for all other chronic conditions.[5]

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[1] Office of Disease Prevention and Health Promotion, Mental Health and Mental Disorders, at: https://www.healthypeople.gov/2020/topics-objectives/topic/mental-health-and-mental-disorders.
[2] S. Pal, Incidence and Prevalence of Major Neurologic Disorders. US Pharm, at: https://www.uspharmacist.com/article/incidence-and-prevalence-of-major-neurologic-disorders
[3] Alzheimer's Association, Facts and Figures, at: https://www.alz.org/alzheimers-dementia/facts-figures.
[4] Information Technology & Innovation Foundation, A Trillion-Dollar Opportunity: How Brain Research Can Drive Health and Prosperity, at: http://www2.itif.org/2016-trillion-dollar-opportunity.pdf?_ga=2.209915987.77733799.1607703298-1777725734.1607703298.
[5] Center for Medicare & Medicaid Services Chronic Conditions Utilization/Spending State Level: All Beneficiaries 2017. The average per capita spending for a chronic condition is $22,099.

The high prevalence of these diseases means that nearly every family in the United States has either personally experienced a brain disease or watched a loved one struggle with the effects of diseases like substance use disorder, schizophrenia, multiple sclerosis, Alzheimer's disease, and hundreds of other diseases that impact the brain.

Despite the tremendous human and financial burden of brain and CNS diseases, disorders, and injuries, the discovery and approval of safe and effective treatments for these disorders lags behind other conditions. For that reason, the ABC and more than 100 other brain health partner organizations support the creation of a Neuroscience Center of Excellence (NCOE) at the Food and Drug Administration (FDA).[6] A NCOE will encourage innovation in the study, creation, and regulation of treatments and cures for brain diseases, disorders, and injuries.[7]

To respond to the unique challenges in the discovery and development of treatments for brain disease, and allow more neuroscience discoveries to directly benefit patients, it is vital that the federal government prepare the brain-specific regulatory tools and guidelines needed for fast, well-structured, transparent, and predictable product review. **To support this aim, ABC and the brain community urge Congress to create a NCOE at the FDA. While we understand that the existing authorities in the initial 21st Century Cures legislation allows for FDA to create such a center without Congressional direction, we believe that Congressional direction and funding for a center will provide the urgency needed for FDA to move quickly to establish an NCOE. We believe a NCOE will foster innovation in the regulation and development of treatments for brain diseases, disorders, and injuries.**

Several pieces of existing legislation address the need for a NCOE at the FDA. First, we are pleased that the Committee is considering H.R. 6000, the Cures 2.0 Act today. H.R. 6000 contains language (Section 306) to authorize a new intercenter institute at the FDA focusing on high prevalence and burdensome diseases, like those affecting the brain and CNS. As an option for authorizing a NCOE we encourage the committee to advance H.R. 6000, including Section 306.

The ABC also supports H.R. 5435, the Bringing Regulatory Advances Into Neuroscience (BRAIN) Act, a bipartisan bill that would establish, and authorize funding for, a NCOE and create Neuroscience Translational Working Group. The composition of the Working Group would reflect the entire stakeholder community, including patients and their families. The Working Group would provide invaluable "boots on the ground" community experience to help inform the NCOE's work and decisions on 1) translating neuroscience discoveries into approved treatments, 2) developing guidance documents to expedite novel approaches to cures and therapies, 3) creating useful and fruitful collaboration opportunities across governmental entities and public-private partnerships. The Working Group would provide vital information to the NCOE on patient preferences and patient-reported outcomes, along with real-world data for the development of and likely impact of treatments on patients' lives.

Importantly, the BRAIN Act follows the model of the 21st Century Cures Act, which led to the creation of the Oncology Center of Excellence, by giving the FDA the flexibility needed to respond to emerging science and patient input. Rather than delineating specific activities in legislative text, the BRAIN Act

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[6] Letter to Congresswoman Diana DeGette and Congressman Fred Upton regarding the creation of a Neuroscience Center of Excellence, at: https://drive.google.com/file/d/1gZ7wRPvdDqfiaYaZBGMv3oETAo45tENW/view.

[7] H. Gellis, et. Al. Incentivizing Drug Development for Serious Mental Illness. Tufts Center for the Evaluation of Value and Risk in Healthcare, at: https://drive.google.com/file/d/1OeNwcQ3H_YOTKX_QGBpVUEdR5eVFcLX1/view.

relies upon existing regulatory mechanisms for the FDA to obtain patient, researcher, and industry input on its activities, allowing the agency to adapt quickly to an evolving field of research and development. This structure, and its expansion to brain diseases and disorders, is supported by more than 80 organizations, former FDA Commissioner Scott Gottlieb and current FDA Commissioner Robert Califf.[8]

Related legislation has also been recently introduced in the Senate. Like the BRAIN Act, S. 3427, the Neuroscience Center of Excellence Act, would create, and authorize funding for, a NCOE. S. 3427 includes provisions that would help improve patient engagement and speed the delivery of treatments to patients who desperately need them. For instance, S. 3427 acknowledges the need for patient engagement with the inclusion of the Neuroscience Patient-Focused Drug Development Program and a study to assess the patient experience in medical products for brain and central nervous system diseases and disorders. Public input, including patient engagement, should be a requirement for all activities carried out by the NCOE.

ABC also supports the requirement in S. 3427 for the NCOE to hold annual public meetings to seek input from scientists, researchers, patient advocacy organizations, disease research organizations, and the drug and device industry. We recommend the issues discussed during these meetings be determined by FDA in partnership with patients and relevant industry and research partners. This will allow the agency to focus on emerging science and timely needs in the neuroscience space. Last, ABC supports the provision in S. 3427 requiring the FDA to issue guidance to industry on how to ensure greater diversity in clinical trials for medical products to treat diseases, disorders, and injuries of the brain and central nervous system.

As the committee considers proposals for inclusion in upcoming FDA user fee legislation, **ABC strongly encourages you to incorporate language to establish a NCOE**. Each of the existing legislative proposals contains provisions that would be of tremendous benefit to the millions of patients suffering from brain and CNS diseases, disorders, and injuries. Of most importance is ensuring that FDA has the flexibility to respond to advancing science and innovation as neuroscience discoveries emerge.

Again, thank you for the opportunity to provide this statement. The ABC looks forward to working together with the committee toward advancements that improve the health of all people living with brain and CNS diseases, disorders, and injuries.

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[8] Letter to Congressman Earl Blumenauer, Congressman Bill Pascrell, and Congressman Don Bacon regarding the BRAIN Act, at: https://drive.google.com/file/d/1_cDLk1SlRhnWyNFjub907SXOQcyWp84i/view; shorturl.at/ltyMX

Statement of the EveryLife Foundation for Rare Diseases

House Energy & Commerce Subcommittee on Health Hearing:
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

March 17, 2022

Chairwoman Eshoo, Ranking Member Guthrie and Members of the Committee: The EveryLife Foundation for Rare Diseases applauds you for convening this hearing to explore a number of legislative proposals intended to accelerate innovation of therapies, while ensuring appropriate levels of oversight. For nearly 15 years, the EveryLife Foundation for Rare Diseases has existed as a catalyst for the rare and ultra-rare patient and caregiver voice to work with legislators, including your Subcommittee, to achieve these goals.

The EveryLife Foundation was created to help advance the needed research that can lead to the development of treatments for the thousands of rare and ultra-rare diseases and conditions that today lack therapies. In the four decades since the passage of the landmark Orphan Drug Act, we have made significant progress in developing treatments for rare diseases. This progress has accelerated in recent years, with drugs designed to treat a rare disease or condition accounting for nearly 60 percent of products approved in 2020 by the Center for Drug Evaluation and Research (CDER). Despite these improvements, the painful reality is that more must be done for the majority of patients with rare diseases or conditions who have no disease-modifying therapies. As of today, only about 5% of the more than 7000 rare diseases have approved therapies. And of those with approved therapies, even fewer have proven to be curative. Our community is in dire need of innovations that match the urgency and unmet need of the Americans living with rare diseases[1].

Recognizing this reality, the EveryLife Foundation strongly supports a number of bills that are the subject of today's hearing beginning with H.R. 1730, the Speeding Therapy Access Today (STAT Act). The Foundation applauds Congressman Bilirakis and Congressman Butterfield for sponsoring this legislation and thanks the dozens of cosponsors for their support, including Energy & Commerce Committee Members, Lesko, Soto, Joyce, and O'Halleran. We also commend Senators Amy Klobuchar and Roger Wicker for leading the Senate companion bill (S. 670), and we hope today's hearing continues to move the STAT Act towards being enacted into law this Congress.

The EveryLife Foundation was privileged to work closely with our sponsors and committee staff over many months to develop this bill. The guiding objective was identifying a targeted set of provisions that, if enacted, could make a sizeable impact in accelerating development of rare disease treatments. With this in mind, we offer the following comments on specific components of this legislation.

Rare Disease Center of Excellence: A core piece of the STAT Act is the explicit authorization of a Food and Drug Administration (FDA) Intercenter Institute or Center of Excellence focused on rare diseases. This provision builds upon the authorization for such institutes contained in the 21st Century Cures Act and authorizes one focused on rare diseases and conditions. This provision seeks to build upon FDA's existing commitments to rare disease, particularly within CDER, by creating an FDA-wide function to house and further grow the agency's rare disease expertise. The aim is to ensure that such expertise is not siloed in a single review division or center and to apply the knowledge and learnings to rare disease needs wherever they lie in FDA. The goal is to prevent unnecessary duplication of resources and to further develop agency knowledge and expertise, particularly in the area of ultra-rare diseases, including trial design and trial metric for small population trials, manufacturing standards for small population therapies, overlapping or concurrent approaches to preclinical activities, and other regulatory science needs.

The STAT Act recognizes that FDA Centers of Excellence are not one-size-fits-all. As such, a Rare Disease Center of Excellence will not look exactly like the Oncology Center or any other existing center. Additionally, review and approval authority will continue to rest with the center and the divisions to which a candidate therapy is assigned.

The EveryLife Foundation has spent extensive amounts of time and resources on the concept of a Rare Disease Center of Excellence with thinking coming from all rare disease stakeholders including patients, clinicians, researchers, and manufacturers. We believe this concept builds upon FDA's actions over the past several years and that it presents the most appropriate model for housing all of FDA's rare disease expertise in a single home and for continuing to build and expand this regulatory knowledge and these capabilities. We have included a copy of a recently released white paper detailing the rationale and vision for a Rare Disease Center of Excellence along with today's statement.

Ultra-Rare Disease Focus: As noted above, the STAT Act also includes authorization of a specific program within the Center, known as the ALTITUDE Program, that focuses explicitly on the unique needs associated with therapies to treat very rare disease or conditions. We believe that this focus is necessary, given the many unique regulatory science needs associated with developing treatments for very small populations and, in some cases, for individuals. A focus on this set of issues will hopefully become even more necessary over the coming years as the benefits of precision medicine continue taking hold.

Labels of Rare Disease Therapies: The rare disease community has unfortunately encountered challenges in obtaining access to affordable rare disease therapies that are in line with the FDA's label for these therapies. This has been because of actions taken by payors to inappropriately limit access by narrowing the eligible population beyond what is indicated in the FDA-approved label. For example, in some instances, payors have authorized a treatment only for those patients who match the criteria of the population included in the clinical pivotal trial even when FDA's label is broader.

The EveryLife Foundation recognizes that few issues are as complex and important as a product's FDA label. That's why we support this provision within STAT that calls for FDA to organize a multi-stakeholder group to convene on this topic and produce a guidance document. Rather than prescribe an outcome in legislation, this provision simply authorizes a stakeholder and guidance process, in line with provisions in other laws such as multiple provisions in the 21st Century Cures Act. We believe that FDA needs to hear directly from stakeholders on both these challenges and potential solutions to address them.

Early Engagement of Payors: Building upon the comments above, the EveryLife Foundation recognizes that early conversations between therapy developers and payors is critical to achieving appropriate access, particularly for novel first-generation medications. We note that FDA's device center has an all-payor early feedback program to facilitate conversations between developers and payors on topics that can help lead to positive coverage decisions. We believe a similar early-payor feedback program is desperately needed for rare disease needs and that having these conversations early can help prevent or reduce post-approval coverage decisions that inappropriately limit patient access to therapies.

The EveryLife Foundation strongly supports this provision within the STAT Act that authorizes such a program and requires regular reporting on the impact of the program. We note that it is modeled upon the existing and successful CDRH program, which provides an important precedent for a rare disease-focused program within FDA. While it will be important to ensure appropriate guardrails are in place to preserve the distinct authorities afforded to FDA and CMS, we need a similar program to encourage and support dialogue with payors focused on rare diseases.

Rare Disease Advisory Committee: Given the myriad policy issues of interest to the rare disease community, the EveryLife Foundation strongly supports the provision within the STAT Act that would establish a Rare Disease and Condition Drug Advisory Committee. We see a significant need for assembling such a panel of external advisors to provide FDA with additional expertise and perspective in this field, but also not act as an additional obstacle to the drug review process. We note that FDA maintains a number of advisory committees that provide advice and counsel on cross-cutting issues that apply to multiple topics. Existing advisory committees of this nature include the Pediatric, Patient Engagement, and Risk Communication advisory committees.

An advisory panel on rare diseases and conditions would provide FDA with the external expertise needed to advise on both pending new drug applications – in tandem with the relevant human drug advisory committee – as well as on larger topics of relevance to the field, such as innovative trial designs for small populations and use of real-world evidence (RWE) to help satisfy post-approval requirements. We strongly support authorization of such a committee as a component of the STAT Act.

Funding to Support Rare Disease Regulatory Science Research: The EveryLife Foundation recognizes that there is a need to continue building the body of knowledge associated with rare

diseases and conditions. The Foundation has routinely supported efforts to increase appropriations for existing programs that help fund orphan drug clinical trials as well as rare disease natural history studies. We believe additional needs exist, including support for regulatory science activities pertaining to development of therapies to treat very small populations. As such, we strongly support the provision within STAT that authorizes such regulatory science research.

Other Legislation

In addition to the STAT Act, the EveryLife Foundation is pleased that the hearing will include other bills of interest to the rare disease community. These include:

- The Cures 2.0 Act, H.R. 6000, which would include authorization of a rare disease Center of Excellence and contains several other rare disease-focused provisions;

- The Helping Experts Accelerate Rare Treatments (HEART) Act, H.R. 6888, which would enhance reporting on rare disease activities and authorize a GAO study of the European Union's best practices in handling rare disease applications; and

- The Better Empowerment Now to Enhance Framework and Improve Treatments Act of 2021 (BENEFIT) Act, H.R. 4472, which would build upon existing law and policies to ensure patient experience data is fully reflected as part of FDA's benefit-risk regulatory framework.

- The Advanced Research Project Agency-Health (ARPA-H) Act, H.R. 5585, which would establish a new, collaborate agency within the Department of HHS to catalyze the development of high-impact, novel treatments, diagnostics, cures, and preventative measures for communities with significant unmet need.

- The Diversifying Investigations Via Equitable Research Studies for Everyone Trials (DIVERSE) Act, H.R. 5030, and the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, H.R. 6584, which would enhance clinical trial diversity by decentralizing trials and making participation easier and more accessible.

We urge the Committee to promptly move forward with markups on each of these bills so that like the STAT Act they can become law this Congress.

Comments on Accelerated Approval

The EveryLife Foundation recognizes the ongoing discussions pertaining to the utilization of the Accelerated Approval (AA) pathway and support evidence-based approaches to protect and strengthen this life-saving regulatory pathway. The AA pathway is an FDA review pathway limited to treatments for serious and often fatal illnesses with few, if any, options in which therapy development is based upon

validated surrogate endpoints, backed by science. The rare disease community is grateful to Congress for the creation of a regulatory pathway that enables approvals based on surrogate endpoints that can often more accurately capture real-time disease progression or improvement, while requiring the same regulatory standard for approval as is applied to all regulatory reviews.

We recognize the importance of ensuring that post-approval confirmatory studies are conducted in a timely manner, while acknowledging that the complexities of rare disease therapy development further complicate the design and implementation of such studies. We further recognize the concerns of payors – including public payors – about situations in which such studies are delayed for lengthy periods of time, and we believe patients deserve to know that a therapy is indeed efficacious.

As Congress considers legislation to strengthen the Accelerated Approval pathway, we caution against any actions that could undermine the intent of the program and exacerbate situations in which payors refuse to cover drugs approved under the pathway. Policies that regard Accelerated Approval medications as experimental may only further exacerbate health inequity among communities eligible for potentially life-altering and lifesaving medications. As the Institute for Clinical and Economic Review (ICER) noted in its April 2021 whitepaper, more than 75 percent of drugs approved from 1992 to 2016 via the Accelerated Approval pathway converted to full approval.

EveryLife supports provisions that would improve transparency and reporting on post-approval studies. We also support clarifying the statute further to include the use of RWE to satisfy confirmatory study requirements. Additionally, we note that executing confirmatory studies in rare disease populations is often complex and that additional guidance and direction on this topic, as well as earlier formalized engagement between FDA and sponsors around confirmatory trial design are needed to facilitate such studies in a timely manner. We urge Congress to recognize this reality and to not take any actions that could jeopardize the use of this pathway for the rare disease community going forward. Ultimately, the Foundation supports making the necessary reforms without undercutting access to this pathway.

Conclusion

In closing, the EveryLife Foundation for Rare Diseases thanks you again for convening this legislative hearing and for considering the STAT Act and other rare disease-focused bills on the agenda. We urge the committee to promptly move toward subcommittee and full committee markups of the STAT Act and the other legislation we have endorsed. And we stand ready to assist the committee as you continue considering these and other policies relevant to all impacted by rare disease.

1. https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs

emulate

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

27 Drydock Avenue 5th Floor
Boston, MA 02210

Testimony of
Jim Corbett, CEO Emulate, Inc.
Before the Subcommittee on Health of the Committee on Energy and Commerce
Thursday, March 17, 2022
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

On behalf of Emulate, Inc., the leading provider of organ-on-a-chip technology, I offer this testimony in support of the FDA Modernization Act of 2021 (H.R 2565 and S. 2952).

Since the Federal Food, Drug, and Cosmetics Act (FFDCA) of 1938 mandated that all new drugs be tested for toxicity in animals prior to human studies, scientific advancements have been abundant. However, predicting human toxicity through animal models still leaves us with a public health issue.

There is no doubt that animal models have contributed to major advances in medicine and have contributed to safe and effective drugs making it to market. However, these models have the difficult job of approximating the human body, and sometimes they get it wrong.

A growing body of evidence suggests that animal models are lacking in both sensitivity and specificity when it comes to predicting drug toxicity in humans.[1-3]

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A 2014 study analyzing the effects of 2,366 drugs in both animals and humans found that "tests on animals (specifically rat, mouse and rabbit models) are highly inconsistent predictors of toxic responses in humans and are little better than what would result merely by chance."[4] A 2008 review found similar results, concluding that animal models predicting drug toxicity in humans may have sensitivity and specificity values below 70%.[2]

The cost of poor specificity and selectivity is too often passed onto the patient. A review of 578 discontinued and withdrawn drugs in Europe and the United States showed that nearly half halted distribution due to post-approval toxicity.[5] Similarly, a 2012 analysis of 93 post-approval drugs with serious toxicity effects found that only 19% of them showed indications of toxicity in animal studies.[6]

In a recent study published to bioRxiv, researchers found the human Liver-Chip to have an 87% sensitivity and 100% specificity when differentiating hepatotoxic from non-hepatotoxic small molecules.[7] Importantly, all 22 hepatotoxic drugs included in the study had previously been classified as safe due to a lack of toxicity in animal models. Collectively, these compounds resulted in 208 patient fatalities and 10 liver transplants. Had the human Liver-Chip been used during preclinical screening of these compounds, it's likely that many of these fatalities could have been avoided.

Animal models have played an undeniably significant role in the evolution of medicine, and will continue to do so, but to make the drug development process safer, more efficient, and more humane, we must take a hard look at

how we can leverage scientific advancements to continuously improve patient safety.

Sincerely,

Jim Corbett
CEO
Emulate, Inc.

1. Van Norman GA. Limitations of animal studies for predicting toxicity in clinical trials: Is it time to rethink our current approach? *JACC Basic Transl Sci*. 2019;4(7):845-854. 2019. doi: 10.1016/j.jacbts.2019.10.008
2. Matthews RA. Medical progress depends on animal models - doesn't it? *J R Soc Med*. 2008;101(2):95-98. doi: 10.1258/jrsm.2007.070164
3. Not-OD-12-025: NIH research involving chimpanzees. National Institutes of Health. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-025.html. Accessed December 17, 2021.
4. Bailey J, Thew M, Balls M. An analysis of the use of animal models in predicting human toxicology and Drug Safety. *Altern Lab Anim*. 2014;42(3):181-199. doi: 10.1177/026119291404200306
5. Siramshetty VB, Nickel J, Omieczynski C, Gohlke BO, Drwal MN, Preissner R. WITHDRAWN--a resource for withdrawn and discontinued drugs. *Nucleic Acids Res*. 2016;44(D1):D1080-D1086. doi: 10.1093/nar/gkv1192
6. van Meer PJK, Kooijman M, Gispen-de Wied CC, Moors EHM, Schellekens H. The ability of animal studies to detect serious post marketing adverse events is limited. *Regul Toxicol Pharmacol*. 2012;64(3):345-349. doi: 10.1016/j.yrtph.2012.09.002
7. Ewart, Lorna, et al. Qualifying a Human Liver-Chip for Predictive Toxicology: Performance Assessment and Economic Implications. 16 Dec. 2021, 10.1101/2021.12.14.472674. Accessed 8 Mar. 2022.

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Boston, MA 02210

March 16, 2022

The Honorable Frank Pallone
U.S. House of Representatives
237 Cannon House Office Building
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
U.S. House of Representatives
1035 Longworth House Office Building
Washington, DC 20515

Dear Chairman Pallone and Ranking Member McMorris Rodgers,

We write today to convey our strong support for FDA's Accelerated Approval pathway and to convey to Congress the importance of preserving and strengthening this critical tool for bringing therapies to patients currently living with unmet medical need. At each turn when Congress has legislated on accelerated approval the pathway has been reaffirmed and the Agency has been encouraged to fully harness the promise of the pathway on behalf of patients. Lives have been saved, extended and improved.

Millions of American families are grateful for these past actions by Congress and fully expect this Congress to continue to support and encourage the use of accelerated approval for all of the patients who today live with unmet medical needs. Who are these patients? They are Americans living with rare diseases, 95% of which currently have no approved treatments. They are Americans living with conditions like Alzheimer's where treatments are just beginning to emerge but the unmet need remains vast or diabetes where treatments have emerged but there are still unmet needs in disease modifying therapies to address the underlying autoimmunity in type 1 diabetes. They are Americans, many of whom are children, whose disease progression means that the loss of certain core functions and mobility cannot be recovered if novel therapies take too long to clear the regulatory process. They are Americans for whom a curative treatment is on the horizon through game changing cell and gene therapies. And the list goes on.

As you begin consideration of the FDA User Fee reauthorization the undersigned organizations and our broader community of patients and families wants to be clear about our unequivocal support for preserving the accelerated approval pathway and ensuring that all patients living with unmet need, regardless of their specific condition, can continue to have confidence in the FDA's utilization of the pathway.

We stand ready to support any effort you may undertake to reaffirm Congress' ongoing support for accelerated approval. Just as we stand ready to support those efforts, we also stand ready to defend the pathway against any efforts that would intentionally or unintentionally limit FDA's ability to utilize the pathway or any efforts that would essentially undermine the use of or confidence in the pathway. HIV went from a death sentence to a chronic disease because of accelerated approval. Many cancers have been beaten back due to accelerated approval. It is

only reasonable to continue to offer that same hope and deliver on the same results for the millions of patients still living with unmet need.

Sincerely,

Robert Egge
Chief Public Policy Officer, Alzheimer's Association
Executive Vice President, Alzheimer's Impact Movement

Cynthia Rice
Chief Mission Strategy Officer, JDRF

CC:

Rep. Bobby Rush
Rep. Anna Eshoo
Rep. Diana DeGette
Rep. Michael Doyle
Rep. Janice Schakowsky
Rep. G.K. Butterfield
Rep. Doris Matsui
Rep. Kathy Castor
Rep. John Sarbanes
Rep. Jerry McNerney
Rep. Peter Welch
Rep. Paul Tonko
Rep. Yvette Clarke
Rep. Kurt Schrader
Rep. Tony Cardenas
Rep. Paul Ruiz
Rep. Scott Peters
Rep. Debbie Dingell
Rep. Marc Veasey
Rep. Ann Kuster
Rep. Robin Kelly
Rep. Nanette Diaz Barragan
Rep. Donald McEachin
Rep. Lisa Blunt Rochester
Rep. Darren Soto
Rep. Tom O'Halleran
Rep. Kathleen Rice
Rep. Angie Craig
Rep. Kim Schier
Rep. Lori Trahan
Rep. Lizzie Fletcher
Rep. Fred Upton
Rep. Michael Burgess
Rep. Steve Scalise
Rep. Robert Latta
Rep. Brett Guthrie
Rep. David McKinley
Rep. Adam Kinzinger
Rep. Morgan Griffith
Rep. Gus Bilirakis
Rep. Bill Johnson
Rep. Billy Long
Rep. Larry Bucshon
Rep. Markwayne Mullin
Rep. Richard Hudson
Rep. Tim Walberg
Rep. Earl Carter
Rep. Jeff Duncan
Rep. Gary Palmer
Rep. Neal Dunn
Rep. John Curtis
Rep. Debbie Lesko
Rep. Greg Pence
Rep. Dan Crenshaw
Rep. John Joyce
Rep. Kelly Armstrong

October 20, 2021

Dear Congresswoman Eshoo:

We, the undersigned, commend you for introducing the Advanced Research Projects Agency for Health (ARPA-H) Act (H.R. 5585), a bill that would authorize an important conduit for bold new health innovations. Under your legislation, ARPA-H would be positioned to empower high risk, high reward strategies aimed at rapidly accelerating medical and public health progress. We share the commitment you, other champions in Congress from both sides of the aisle, and the Administration have made to make ARPA-H a success.

We appreciate your determination to stand up ARPA-H as soon as possible and equip it with the flexibility and authorities it needs to meet its unique mission. We offer ourselves as a resource as you continue to refine the legislative text and work towards authorizing the creation of ARPA-H this year.

Thank you for your longstanding leadership as a steward of forward-thinking, patient-centric health policy, and for the crucial role you are playing in advancing ARPA-H. We look forward to working with you, your colleagues in Congress, and the Administration to make this unique medical innovation incubator a reality.

Sincerely,

George Vradenburg
Co-Founder and Chair
UsAgainstAlzheimer's

Christopher Austin, MD*
Founding Director
National Center for Advancing Translational Sciences

Cartier Esham, PhD
Chief Scientific Officer
Biotechnology Innovation Organization

Annie Kennedy
Chief of Policy, Advocacy, and Patient Engagement
EveryLife Foundation for Rare Diseases

Amy Comstock Rick, JD*
President and Chief Executive Officer
Food and Drug Law Institute

Mary Woolley*
President and Chief Executive Officer
Research!America

Keith R. Yamamoto, PhD*
Vice Chancellor for Science Policy and Strategy, UCSF
Director, UCSF Precision Medicine
Professor, Cellular & Molecular Pharmacology

Ellen Sigal
Founder and Chairperson
Friends of Cancer Research

John Dwyer
President
Global Alzheimer's Platform Foundation

Margaret Hamburg, MD*
21st Commissioner
U.S. Food and Drug Administration

Sudip Parikh, PhD*
Chief Executive Officer
American Association for the Advancement of Science

Andrew C. von Eschenbach, MD
President, Samaritan Health Initiatives
12th Director, National Cancer Institute
20th Commissioner, U.S. Food and Drug Administration

Bob Wright
Founder and Chair
The Suzanne Wright Foundation

*Denotes those signing in their individual capacity. Organization included for identification purposes only.

P.O. Box 544
Ambler, PA 19002
215.325.1306

March 15, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Testimony of

NATIONAL FOUNDATION FOR CELIAC AWARENESS dba BEYOND CELIAC

Before the Subcommittee on Health, Committee on Energy and Commerce

Thursday, March 17, 2022

The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

BEYOND CELIAC supports the FDA Modernization Act because it would:

- Authorize the use of the best nonclinical test methods, animal-based or human-based, to determine the safety and efficacy of a new drug, whether animal or nonanimal.
- Broaden options for drug sponsors to use test methods most likely to predict how a drug will react in humans, including state of the art nonclinical models based on human biology.
- Encourage innovation and use of 21st Century science to improve success in clinical trials, bring more treatments to patients sooner and at less cost.

Nancy D. Ginter
Director of Administration
Beyond Celiac
nginter@beyondceliac.org

national lgbt cancer network
ADVOCATING FOR HEALTH EQUALITY

March 15, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Testimony of
National LGBT Cancer Network
Before the Subcommittee on Health, Committee on Energy and Commerce
Thursday, March 17, 2022
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

National LGBT Cancer Network supports the FDA Modernization Act because it would:

- Authorize the use of the best nonclinical test method, animal-based or human-based, to determine the safety and efficacy of a new drug, whether animal or nonanimal.
- Broaden options for drug sponsors to use test methods most likely to predict how a drug will react in humans, including state of the art nonclinical models based on human biology.
- Encourage innovation and use of 21st Century science to improve success in clinical trials, bring more treatments to patients sooner and at less cost.

Sincerely,

Scout, Ph.D.
Executive Director

March 15, 2022

RE: Growth of Drug-Resistant Fungi Threatens Health in the U.S.

Dear Members of Congress and health legislative staff:

We write to you out of concern for the growing threat of drug-resistant fungal infections here in the United States and internationally. Recent findings suggest that front-line medications no longer work for certain kinds of fungal infections here in the US and Americans with severe COVID-19 are particularly vulnerable. Fungal drug resistance also contributes to other serious health threats like antimicrobial resistance. When left untreated, invasive fungal disease is nearly always associated with death. Fungal infections are a global threat that is becoming increasingly severe. Annually, over 150 million severe cases of fungal infections occur worldwide resulting in approximately 1.7 million deaths.[1] With these considerations in mind, federal government should prioritize antifungal and antibiotic drug development as a priority for pandemic preparedness to get ahead of these problems.

The global emergence of antifungal resistance is a growing threat to public health. Research released just before the onset of the COVID-19 pandemic suggest that the threat of drug-resistance for patients with a fungal infection is increasing.[2] This threat is present and all too real in the United States. As an example, the US burden of invasive candidiasis including bloodstream infection is more than 70,000 people, with a global burden of more than 750,000 people.[3] Transplant recipients, diabetes patients, premature infants, and patients in intensive care are at highest risk of contracting these types of infections. About 7% of all Candida blood samples tested at CDC are resistant to the antifungal drug fluconazole; in parallel, resistance to echinocandins (the other class of drug used to treat Candida infections) also appears to be increasing, especially in the species Candida glabrata. Patients with Candida infections that are resistant to both fluconazole and echinocandin drugs have very few treatment options. In particular, concern is rising over the growing threat of the fungus *Candida auris* in the United States. In fact, roughly 90% of *Candida auris* samples were found to be resistant to fluconazole and as many as one-third resistant to other drugs that can treat the infection.[4]

We also learned some disturbing news in 2021 that the threat is getting worse.

The CDC released findings in June 2021 that "researchers have for the first-time reported cases of people carrying or infected with strains of the dangerous fungus *Candida auris* that were resistant to all major classes of antifungal drugs before any treatment. The CDC reported on five cases, three in Washington, D.C., and two in Texas. The agency also reported evidence of some transmission of the strains within health facilities. That there are now so-called pan-resistant cases in people who had never been treated with antifungal drugs is particularly unnerving, experts said."[5] Late last year, the CDC also released a warning that "people with

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[1] Fungal infections in humans: the silent crisis - PMC (nih.gov)
[2] Antifungal Resistance: a Concerning Trend for the Present and Future | SpringerLink
[3] Toda M; Williams SR; Berkow EL. et al. Population-Based Active Surveillance for Culture-Confirmed Candidemia — Four Sites, United States, 2012–2016. US Department of Health and Human Services/Centers for Disease Control and Prevention. MMWR / September 27, 2019 / Vol. 68 / No. 8
[4] Antifungal Resistance in Candida | Fungal Diseases | CDC
[5] US sees first Candida auris cases resistant to all drugs in untreated people (statnews.com)

severe COVID-19, such as those in an intensive care unit (ICU), are particularly vulnerable to bacterial and fungal infections." In fact, one study found that COVID-19 and influenza patients who are admitted to intensive care or developed acute respiratory distress syndrome are at an increased risk for secondary life-threatening invasive aspergillosis infection.[6] These fungal co-infections are being reported with increasing frequency and can cause severe illness and death.

We, the undersigned, stand united in our efforts to protect American patients from this growing threat. New drug and vaccine development, along with improved diagnostic and other proper stewardship efforts, will be needed to head off what we fear is another emerging pandemic health threat – and should be prioritized by Congress this year. The PASTEUR Act, sponsored by Senator Bennet, Senator Young, Representative Doyle, and Representative Ferguson, would allow us to take a big step forward in the fight against fungal infections, and we urge Congress to prioritize this legislation as part of pandemic preparedness legislative efforts. In addition, the FORWARD Act, sponsored by Representative McCarthy, Representative Bass, Representative Schweikert, Representative O'Halleran, Senator Kelly, Senator Sinema, and Senator Feinstein includes meaningful proposals for desperately needed work on other medically threatening fungi. Taken together, these pieces of legislation represent important and effective actions to address the growing fungal infection crisis.

Sincerely,

Abgenics Life Sciences Pvt Ltd
Acurx Pharmaceuticals
Aequor Inc.
Amgen
AMR Action Fund
AMR.Solutions
Analytika
Antibiotic Resistance Action Center, the George Washington University
Anti-infectives Consulting
Appili Therapeutics, Inc.
Aridis Pharmaceuticals
Arixa Pharmaceuticals
ARM! Antimicrobial Research Matters!
Bactria Pharmaceuticals, LLC
Basilea Pharmaceutica International Ltd
bioMerieux Inc.
Biotechnology Innovation Organization (BIO)
Center for Emerging and Neglected Diseases, UC Berkeley
Centre to Impact AMR
Children's Memorial Hermann Hospital
Connecting Pharma BV
CUBRC, Inc.

[6] Rutsaert L, et al. COVID-19-associated invasive pulmonary Aspergillosis. Ann Intensive Care. 2020;10(1):71. https://doi.org/10.1186/s13613-020-00686-4

Cystic Fibrosis Foundation
Developing Novel Antibiotics Consultancy
Doctor of Choice
Eastern Michigan University
F2G, Inc.
Felix Biotechnology
Gravitas Therapeutics, Inc.
Hospital Maisonneuve Rosemont
HealthyWomen
Hearts Consulting Group, LLC
Hill Scientific and Public Affairs, LLC
Houston Methodist Hospital
Infectious Diseases Society of America (IDSA)
Institute for Advanced Clinical Trials for Children
Institute for Life Science Entrepreneurship
Instituto de Salud Carlos III
Invitris
JMI Laboratories
Kathera Bioscience, Inc.
KAU
Labcorp
RNA Medicines, LLC
McCarthy Consultants, Inc.
Medical University of Vienna
Memorial Hermann
Midwestern University
Monash University
Mycoses Study Group Education and Research Consortium
Mycovia Pharmaceuticals
National Association of Pediatric Nurse Practitioners
Neoculi Pty Ltd
Northeast Pharmaceutical Services, LLC.
Novo Holdings
NTM Info & Research
Omnix Medical
Partnership to Fight Chronic Disease (PFCD)
Partnership to Fight Infectious Diseases (PFID)
Pediatric Infectious Diseases Society
Peggy Lillis Foundation
Q2Pharma
Rutgers University
Scientific and Medical Affairs Consulting
SCYNEXIS

Sepsis Alliance
Sequella, Inc
Shionogi Inc
SIDR Program
Stochos Therapeutics
Stuart B. Levy Center for Integrated Management of Antimicrobial Resistance at Tufts (Levy CIMAR)
Sydney Institute of Infectious Diseases, University of Sydney
Technical University of Munich
The Gerontological Society of America
The Valley Fever Institute at Kern Medical
UC Davis Health
University College London Hospitals, London, United Kingdom
University of Alabama at Birmingham
University of Kansas Medical Center
University of Leeds; Leeds Teaching Hospitals NHS Trust
University of Michigan-Ann Arbor
University of Nizwa
University of Notre Dame
University of Strathclyde
University of Texas Austin
University of Texas Health Science Center at Houston
University of Wisconsin
University of Queensland, Institute for Molecular Bioscience
US Citizen
VA Boston
Valley Fever Center for Excellence, University of Arizona College of Medicine-Tucson
Valley Fever Solutions
Venatorx Pharmaceuticals, Inc.
Washington University in St. Louis
Zavante Royalty Corporation

Individuals:
Gerard Sheehan
John Freund, former CEO of Arixa Pharmaceuticals
Kelly Wright
Kevin Outterson, Boston University
Peter Pappas, MD FACP
Royce H. Johnson, MD FACP
John Perfect, MD
Greg Basarab
Samuel J. Borgert

Valley Fever Institute
at Kern Medical

March 16, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
House Energy and Commerce Committee
272 Cannon House Office Building
Washington, DC 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
House Energy and Commerce Committee
2434 Rayburn H.O.B.
Washington, DC 20515

RE: H.R. 5566 (McCarthy) FINDING ORPHAN-DISEASE REMEDIES WITH ANTIFUNGAL RESEARCH AND DEVELOPMENT ACT OF 2021 (FORWARD ACT of 2021) – SUPPORT

Dear Chairwoman Eshoo and Ranking Member Guthrie:

On behalf of the Valley Fever Institute at Kern Medical we are pleased to express our position of support for H.R. 5566, or the FORWARD Act of 2021, which is aimed at combating Valley Fever. Since the Valley Fever Institute at Kern Medical is located in the epicenter of Valley Fever cases and in the heart of California, we see firsthand the tremendous impact the FORWARD Act will have on the health of our community. This legislation would strengthen research and help advance treatment and vaccine development for Coccidioidomycosis, commonly known as Valley Fever, as well as other orphan endemic fungal diseases.

According to the California Department of Public Health, over the past 10 years in Kern County there have been an average of 2,235 cases of Valley Fever per year with an average of 15 deaths per year resulting from the infection. During an epidemic year, those figures can swell to around 3,000 cases. A record high of 9,286 cases were reported statewide in 2019, with 3,373 cases in Kern County.

Valley Fever is an infectious, but not contagious, fungal disease contracted by inhaling spores of a fungus that grows in the dirt in many areas of the Southwestern United States. The majority of Valley Fever is asymptomatic or mild, with illness resembling the flu or pneumonia. Only 10% of patients will have disease severe enough to seek medical attention and receive a diagnosis. Approximately 1% of patients develop disseminated disease, where the fungus spreads outside the lungs, most commonly to the brain, skin, bones, and joints. For these patients, there is a high risk of lifelong damage or death without treatment. Available drugs can produce substantial clinical benefit; however, treatment is lengthy, expensive, and not always successful. Clinical treatment failure and intolerance are common. There is no current drug that eradicates Valley Fever; an average of 200 patients die from Valley Fever annually. This disease can affect anyone that lives, works, or travels to endemic areas; an elevated risk of occupational exposure exists for those who work outdoors, especially in connection with soil disruption.

Valley Fever Institute
at Kern Medical

The Centers for Disease Control and Prevention (CDC) suggests that Valley Fever is not only a serious illness, but also a costly one. Nearly 75% of people with Valley Fever miss work and school. As many as 40% of people who get Valley Fever need to stay in the hospital. The average cost of a hospital stay for a person with Valley Fever is almost $50,000. With a vaccine to prevent and reduce severity of infection, improvement in available testing, and the development of new antifungal drugs, it is possible to lower the impact of this disease on our community.

For these reasons, The Valley Fever Institute at Kern Medical endorses H.R. 5566 and respectfully urges your Subcommittee's support for this legislation.

Sincerely,

Royce H. Johnson, M.D., F.A.C.P., F.I.D.S.A.
Professor of Medicine
David Geffen School of Medicine at UCLA
Chief, Infectious Disease, Kern Medical
Medical Director, Valley Fever Institute

Valley Fever Institute at Kern Medical | 1700 Mt. Vernon | Bakersfield, CA 93306
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Written Comment

Generation Patient

Submitted to the U.S. House of Representatives
Committee on Energy and Commerce

March 17, 2022

"The Future of Medicine: Legislation to Encourage Innovation
and Improve Oversight"

Generation Patient represents young adults with chronic and rare conditions across the United States. Generation Patient is one of the first and only organizations supporting this unique demographic transitioning into adulthood with lifelong conditions. Our organization is independent and we do not accept any funding from the pharmaceutical, insurance, hospital, or other industries. We appreciate the opportunity to submit a statement for the record and speak to crucial legislation impacting our young adult patient community.

Generation Patient was created and is currently led *entirely* by young adult patients. Our work has touched regions across the U.S. from South Texas to Indiana to California. Through our programs, the Health Policy Lab and the Crohn's and Colitis Young Adults Network, we work to increase the health literacy, patient activation, self-management, and advocacy skills of young adult patients. We have facilitated over 200 virtual meetings over the last couple of years in addition to a variety of programming in higher education, peer support, and health policy education.

As an organization, we are concerned about the lack of inclusion of adolescents and young adults with chronic and rare conditions in clinical trials. For all pieces of legislation discussed today, efforts to diversify clinical trials must explicitly include adolescents and young adult patients. Even with limited research, we know that there are substantial differences among pediatric, adolescent, and adult patient populations in drug disposition and response (Kapogiannis & Mattison, 2008). We appreciate the focus on equity within these bills but would encourage greater specificity for the inclusion of adolescents and young adults.

We are also recommending that any post-market reported data of adolescents and young adults be stratified to include narrower age ranges given this is a distinct developmental period. For example, the FDA Adverse Event Reporting System currently has 18-64 as one demographic, which does not allow for the understanding of how a medical product affects young adults versus adults. We recommend narrowing the range to 18-26. This ensures the inclusion of developmentally different ages, as an 18-year-old body is physically different from that of a 60-year-old. The FDA should develop enrollment target numbers that adequately represent the age demographic spread of the patient population for a particular condition. Further, the FDA should require more stringent enrollment criteria as we believe this will expedite the enrollment of underrepresented demographics rather than relying on the sponsors alone which may take longer.

As part of the Accelerated Approval Integrity Act (H.R. 6963), we are in concordance with post-approval progress report requirements, and without a doubt, these should be

made publicly available. The FDA should also ensure the prompt public release of postapproval information. Patients need and deserve to see this information. We appreciate the authority of the FDA to quickly withdraw an accelerated approval drug to prevent patients from being harmed longer than we should.

We are in full support of the development of a Rare Disease and Drug Advisory Committee under the Speeding Therapy Access Today Act (H.R. 1730). The majority of us at Generation Patient live with a rare disease, so the value to us of patient voices as leading the conversation cannot be understated. We recommend council members maintain the integrity of this important advisory committee by disclosing any conflicts of interest and receiving under $5000 from the pharmaceutical industry. We would appreciate the explicit inclusion of independent patient leaders who will serve in the advisory capacity. We would also like to emphasize the need to include diverse ages as part of this committee. Most of the approximate 7,000-10,000 rare diseases disproportionately impact children, adolescents, and young adults (Tisdale et al., 2021). Thus, we believe that a young adult voice is critical to the advisory committee.

For young adult patients living with potentially lifelong conditions, the development of new therapeutic options is extremely important. Many of us are diagnosed with rare and complex conditions for which limited treatment options are available. Our life and quality of life depend on genuine innovation and the prompt development of alternative treatments. While we need new therapeutics, we also need to ensure the integrity of the clinical trial and post-market process. We hope that all discussions today prioritize patient safety.

Thank you for your time and to all parties for contributing perspectives. We applaud the work of the House Committee on Energy and Commerce in facilitating discussions that directly impact patients. We hope that our perspectives will be weighed heavily as the next generation of independent patient advocates.

Kapogiannis, B. G., & Mattison, D. R. (2008). Adolescents in clinical trials. *Clin Pharmacol Ther*, *84*(6), 655-659. https://doi.org/10.1038/clpt.2008.191

Tisdale, A., Cutillo, C. M., Nathan, R., Russo, P., Laraway, B., Haendel, M., Nowak, D., Hasche, C., Chan, C.-H., & Griese, E. (2021). The IDeaS initiative: pilot study to assess the impact of rare diseases on patients and healthcare systems. *Orphanet journal of rare diseases*, *16*(1), 1-18.

Committee on Energy and Commerce
United States House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

Re: Hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"

March 17, 2022

Dear Chairwoman Eshoo and Ranking Member Guthrie,

The Generics Access Project (GAP) commends the House Energy and Commerce Committee for convening this hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight." GAP represents a number of patient advocacy groups in a concerted effort to improve availability of generic medicines in the United States. We urge Congress to enact common sense legislation that will improve timely access to affordable medicines and expand access to the generic drugs that will help lower costs for America's patients.

The U.S. health care system and its patients have benefited significantly from increased access to generic drugs, which make up nearly 90% of all U.S. prescription volume, but account for only 22% of total prescription drug spending.[1] As a result of this growth, more patients have access to lower-cost medicines, which is driving large savings for the U.S. health care system, totaling $2.2 trillion in the last decade (2010-2019) and $313 billion in 2019 alone.[2]

Congress is presented with a unique opportunity as it continues to work towards lowering drug prices to make important refinements that will improve patient access to medicine. More can be done to increase the approval of both simple and complex generic medicines through an efficient, patient-focused regulatory structure. GAP was encouraged by the comments many members of this Committee raised during the "Food and Drug Administration (FDA) User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics" hearing on February 3rd. Numerous Representatives recognized the importance that generic drugs play in our health care system, and we hope these comments will help guide the Committee as it seeks to shape the innovative future of medicine.

Ensuring Legislative Language Helps Achieve Goals of Generic Drug User Fee Agreement (GDUFA) III

Passed in 2012, Congress intended GDUFA to speed up FDA approval of generic drugs, stimulate competition for branded drugs, and reduce overall drug prices for American patients by collecting industry user fees to support the agency's regulatory review of new generic drug applications. Congress is

[1] IQVIA. (2019). Fact Sheet: Generic Drug and Biosimilar Access and Savings in the U.S. Report. https://accessiblemeds.org/sites/default/files/2019-12/AAM-2019-Generic-Biosimilar-Access-Savings-US-One-Pager.pdf

[2] The Association for Accessible Medicines, (October 2020) 2020 Generic Drug & Biosimilars Access & Savings in the U.S. Report https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pdf

now set to reauthorize the third iteration of this program, known as GDUFA III, following months of unprecedented engagement and input from patient groups.

Proposed GDUFA III improvements include:

- implementing better product guidance practices for new generic drug applicants
- expanding mid-cycle review meeting opportunities
- increasing opportunities for timely regulatory feedback
- focusing attention on first and second generation complex generic approvals

The FDA's GDUFA III commitment outlines needed improvements that will ultimately benefit patients by resulting in more affordable treatment options, increased access to complex therapies for serious and chronic conditions and generating savings for patients and the overall health care system. We urge Congress to enact recommendations that support the proposed goals outlined in the GDUFA III Commitment Letter.

Process Reforms to Address Regulatory Inefficiencies

Complex generic medicines are versions of some of the more complicated and innovative chemical-based medicines on the market. These drugs are considered "complex" due to their formulation, their unique drug-device delivery systems, or because of the complexity of their ingredients. These medicines treat some of the most serious diseases such as schizophrenia, metastatic breast cancer, osteoporosis, and diabetes. As innovative medicines become more complex, we will see more complex generics entering the FDA review process, helping patients have increased access to lower-cost alternatives to brand name drugs.

An area for improvement is to reform the FDA's regulatory program it uses to review and approve complex generics via the 505(b)(2) pathway. This pathway is well suited to review and approve complex medicines but the FDA's approach to issuing therapeutic equivalence (TE) ratings should be improved. When a simple generic drug is approved through the Abbreviated New Drug Application process they are deemed "therapeutically equivalent" to the brand drug and issued a corresponding TE rating that gives pharmacists the ability to substitute a lower-cost option at the pharmacy counter. Congress should consider adjusting the 505(b)(2) pathway to allow for manufacturers to request an automatic TE determination once a complex generic is approved.

Currently, it can take years for a TE rating to be obtained by an eligible complex generic applicant. The TE rating must be requested through an open-ended citizen petition process which has become far less predictable and timely in recent years. Sometimes a TE rating is never assigned, and the generic alternative to the brand name medicine never reaches market leaving patients, health care payers, and our society without access to competition.

S. 1463, the Modernizing Therapeutic Equivalence Rating Determination Act, would fix the process for assigning a TE rating by requiring the FDA to issue a TE rating within 30 days of the product's approval through the 505(b)(2) pathway, when a TE rating is requested by the applicant. This modification would help ensure more generics are able to compete, reduce shortages, and lower out-of-pocket costs in a time when so many patients are struggling to meet their healthcare costs.

We urge Congress to enact legislation that updates the FDA 505(b)(2) complex generic approval pathway so that TE ratings are assigned to applicants within 30 days of an applicant's request. Patients see cost savings when they substitute a high-priced brand-name drug for a less expensive, safe, and therapeutically equivalent alternative.

Conclusion

Thank you for the opportunity to share our comments regarding the important role generics and complex generics play when it comes to lowering costs for American patients. The Generics Access Project stands ready to work with Congress, the Administration, and other stakeholders to enhance the approval of generic drugs, increasing the competition they bring to the drug market, and improving access to lower-cost treatment options for patients. Should you have any questions, please contact Gavin Clingham at gavin@allianceforpatientaccess.org.

Sincerely,

Generics Access Project

Founding Members
Alliance for Patient Access
Allergy and Asthma Network
Asthma and Allergy Foundation of America
Color of Crohn's and Chronic Illness
International Cancer Advocacy Network

NATIONAL MARROW DONOR PROGRAM® BE THE MATCH®

March 17, 2021

The Honorable Frank Pallone
Chairman House Energy and Commerce
United States House of Representatives
Washington, D.C. 20515

The Honorable Cathy McMorris Rodgers
Ranking Member House Energy and Commerce
United States House of Representatives
Washington, D.C. 20515

Dear Chairman Pallone and Ranking Member Rodgers,

On behalf of National Marrow Donor Program® (NMDP)/Be The Match®, thank you for the opportunity to provide our input on today's hearing on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

For over three decades, through a competitively bid contract with the Health Resources and Services Administration, NMDP has been entrusted to operate the federally authorized bone marrow program that matches living unrelated adult donors with patients in need of a life-saving blood cell transplant, designated by Congress as part of the C.W. Bill Young Cell Transplantation Program (Program).

Today, patients in need of a blood cell transplant, without a suitable match within their family, have access to more than 39 million potential donors making a cure a reality for thousands of Americans each year. To date, NMDP has facilitated more than 111,000 transplants and partners with over 190 hospital transplant programs in facilitating transplants.

As trusted leaders in advancing treatments for those facing life-threatening blood cancers and other blood diseases, we provide ground-breaking research, innovative technologies, patient support, and patient education that saves lives. Therefore, we are uniquely positioned to comment on the impacts of this agenda that aims to revolutionize how the United States provides care to patients and finds new and better treatments for diseases.

In honor of our longstanding public-private partnership with several United States government agencies, transplant centers across the country, and academic institutions, NMDP is grateful for the opportunity to provide input on the legislation before you today.

We write in support of the following policies before you:

- **Improving Access to Clinical Trials**
- **Innovations in Telehealth Delivery Beyond the Pandemic**
- **Accelerating Research & Creation of ARPA-H**
- **Pandemic Preparedness Rare Disease Support Program**

Improving Access to Clinical Trials
The goal of improving diversity in clinical trials is aligned with NMDP's vision to democratize cell therapy and advance equal outcomes for all. Clinical trials are a key step in advancing potential new treatments for patients with blood cancers and blood diseases, but these trials are not accessed equally by all patients.

NMDP supports the effort to improve access to clinical trials by covering the cost to travel for clinical trials through NMDP's Jason Carter Clinical Trials Program, which helps patients and families find and join clinical trials.

NMDP supports CURES 2.0's efforts to improve clinicaltrials.gov. NMDP offers a searchable database through the Jason Carter Clinical Trials Search and Support Program, one-on-one support from clinical trial navigators, as well as helpful clinical trial information and resources, such as financial assistance and educational fact sheets. An improved clinicaltrials.gov enhances our ability to provide the most accurate and up-to-date information to the patients we serve.

Additionally, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was created in partnership with the NHLBI, NIK, and NIC because of a critical need for multi-institutional clinical trials focused directly on improving survival for patients undergoing hematopoietic cell transplantation. Since 2001, the BMT CTN has opened more than 30 multi-institutional Phase II and III trials, involved more than 100 transplant centers, and enrolled thousands of patients.

NMDP will continue to work to remove barriers to clinical trial participation for patients with transplant-treatable blood disorders and cancers, and supports H.R. 6000 – CURES 2.0, H.R. 5030 – DIVERSE Trials Act and H.R. 6584 DEPICT Act in their intent to do the same.

Innovations in Telehealth Delivery Beyond the Pandemic
The COVID-19 public health emergency (PHE) has highlighted the need for and importance of telehealth in enabling physicians to care for their patients.

Telehealth services implemented during the PHE greatly improved and expanded access to our patients, whose immune systems are ablated in treatment, by allowing those patients to avoid exposure to infectious pathogens during hospital and clinic visits, when clinically appropriate. Telehealth has also helped improve patient outcomes by making follow-up appointments safer and easier.

We ask that you make permanent these changes to Medicare and Medicaid originating site requirements. A durable telehealth extension will continue to ensure that both patients and their donors can access care when they need it as it takes a community to deliver cures for bone marrow, blood stem cell, and cord blood transplant recipients.

Accelerating Research & Creation of ARPA-H
The public-private collaboration between academic centers and industry, facilitated by the NMDP and CIBMTR, has resulted in improvements in patient outcomes following blood cell transplantation. Such collaborative research includes developing new cell therapies directed at eradicating malignant disease, preventing infection, and treating graft-versus-host disease, the top three causes of patient demise following transplantation.

As leaders in innovative cell therapy, we are pleased to share our support for today's legislation accelerating research:

- **Grants for Novel Trial Designs and Other Innovations in Drug Development:** This type of trial design can be particularly useful in the evaluation of complications following complex medical procedures such as blood stem cell transplant and/or immunotherapy for cancer where

prevention of relapse and/or graft versus host disease is critical for addressing common causes of treatment failure.

- **Increasing Real World Evidence:** While randomized clinical trials remain the gold standard for evaluation of efficacy and safety of novel therapies about the standard of care, real-world evidence captured at the population level is critical for continued surveillance of efficacy and safety of new treatments. This is especially relevant to populations that are typically underrepresented in many clinical trials. Real-world evidence data collection strategies that mandate reporting, like the HRSA Stem Cell Therapeutic Outcomes Database, ensure that nearly all patients are represented providing insights into groups that may be less likely to participate in clinical trials and research in general. NMDP encourage the uniform capture and coding of health information, as it would greatly enhance our ability to leverage real-world evidence.
- **Incentives for Decentralized Trials:** Decentralized trials can increase access to clinical trial care and improve patient outcomes. By allowing for virtual care visits, patients will not need to travel to the center, may not need to take as much time off work, and can lessen the burden for patient caregivers. Trials using telemedicine or other digital technologies have the greatest potential to affect underserved patients.
- **ARPA-H:** NMDP supports the creation of ARPA-H to pursue high-risk/high-reward breakthrough innovations. As leaders in cellular therapy, we have a major role in demonstrating that blood cell transplantation from related and unrelated donors can be used to successfully treat over 70 blood cancers and blood diseases and supports similar efforts to deliver seminal treatments to patients in need of a life-saving cure.
- **Research Investment to Spark the Economy**: NMDP support efforts to study the pandemic, to support blood cancer and blood disease patients in the current pandemic and to prepare for future pandemics. The CIBMTR and BMT CTN are conducting a prospective observational study on the efficacy of SARS-CoV-2 vaccines in transplant recipients and cellular therapy recipients. The CIBMTR is also capturing data on COVID-19 infections and outcomes in the same population. Lessons learned from both will continue to serve the community in the ongoing management of COVID in the setting of transplant and cellular therapy and provide insights into the effective management of immunocompromised patients in future pandemics.

Pandemic Preparedness Rare Disease Support Program
Nearly all of the diseases and disorders that can be treated by blood stem cell transplant qualify as rare diseases. We support policies and programs that support our patients in future pandemics.

NMDP/Be The Match supports the implementation of the policies before you today not only to significantly advance medical innovation, but also to make accessible these innovative therapies to patients regardless of race, place, or circumstance.

Please do not hesitate to contact me with any questions, and thank you in advance for your consideration,

Brian Lindberg
National Marrow Donor Program
Chief Policy Officer, Chief Legal Officer and General Counsel

Statement regarding, H.R. 6207, the Humane Cosmetics Act
to the House Committee on Energy and Commerce,
Subcommittee on Health Hearing on
The Future Of Medicine: Legislation To Encourage Innovation And Improve Oversight
March 17, 2022

On behalf of the Humane Society of the United States and Humane Society Legislative Fund, we are thankful the Energy and Commerce Health Subcommittee is hearing a number of bills related to the Food and Drug Administration (FDA) today. And we'd like to highlight another bill, which will facilitate moving away from outdated methods of animal testing toward more humane and human-relevant new approach methodologies. With 153 bipartisan cosponsors we urge the subcommittee, and the broader Energy and Commerce committee, to consider including H.R. 6207, the Humane Cosmetics Act, in any moving legislative packages. The Humane Cosmetics Act ends new animal testing for cosmetics, but gives FDA the discretion to require new testing if absolutely necessary.

There has been a global trend toward eliminating cosmetic animal testing. Since 2018, eight states have passed laws to prohibit the sale of animal-tested cosmetics (California, Nevada, Illinois, Virginia, Maryland, Maine, Hawaii, and New Jersey). Forty-one countries have now passed laws to end or limit cosmetic animal testing including the member states of the EU, Australia, Colombia, Guatemala, Iceland, India, Israel, Mexico, New Zealand, Norway, South Korea, Switzerland, Taiwan, Turkey, and the United Kingdom. Passage of the Humane Cosmetics Act will align U.S. cosmetics policy across the states and around the globe.

The Humane Cosmetics Act also has broad support from the American public and U.S. cosmetics industry. This legislation was developed in consultation with and is endorsed by the leading national cosmetics trade association, the Personal Care Products Council (endorsement letter included with this statement). PCPC represents 90% of the U.S. cosmetics industry, approximately 600 companies. In addition to support from the trade association, 371 companies have individually endorsed the Humane Cosmetics Act including Unilever, Procter & Gamble, The Body Shop, Lush, and Walgreens.

These companies want to meet the vast consumer demand for cruelty-free products, as polling shows 73% of American voters favor national legislation to phase out the use of animal experiments to test cosmetics[1] and 57% of respondents said that the most important cosmetics packaging claim was "not tested on animals." Finally, the legislation will make U.S. cosmetics companies more competitive globally by allowing their products to be sold in the many countries and states where sale of cosmetics that were tested with animal experiments are banned.

[1] 2013 public opinion poll conducted by Lake Research Partners, commissioned by the HSUS and HSLF.

The Humane Cosmetics Act will: 1) prohibit new animal testing of cosmetics and their components; and 2) prohibit the sale in the United States of cosmetics that have undergone cosmetic animal testing one year after the date of enactment of the bill. It has been carefully drafted to address the realities of a global cosmetics marketplace, while also encouraging cosmetics companies to continue their work to replace animal tests with modern, human-relevant science. To that end, it provides some limited exemptions that may allow for new animal testing including: 1) for ingredients or products considered to be drugs by the FDA; 2) when a cosmetic ingredient poses a specific and serious human health risk; 3) when an animal test is required for an ingredient that is also used in a non-cosmetic product; and 4) to comply with foreign regulatory requirements so long as new animal data is not used to substantiate the safety of the cosmetic in the United States.

In traditional animal tests, rabbits, guinea pigs, mice and rats have substances forced down their throats, dripped into their eyes, or smeared onto their skin before they are killed. These test methods are unreliable predictors of human safety. Different species can respond differently when exposed to the same chemicals. Consequently, animal tests may under- or over-estimate real-world hazards to people. In addition, results from animal tests can be quite variable and difficult to interpret.

Companies can already create great products using thousands of available ingredients that have a history of safe use and do not require new testing. For new ingredients where animal testing may currently be used, many non-animal methods have been, and continue to be, developed. Non-animal methods can combine human cell-based tests and sophisticated computer models to deliver human-relevant results at less cost and in less time than traditional animal tests.

We thank you for considering including the Humane Cosmetics Act in any FDA vehicle and welcome the opportunity to answer any follow up questions the Committee may have or provide additional materials. Please contact Elizabeth Smith at elsmith@hslf.org for more information.

May 19, 2021

The Honorable Patty Murray
Chair
Senate HELP Committee
154 Russell Senate Office Building
Washington, DC 20510

The Honorable Frank Pallone
Chairman
House Energy & Commerce Committee
2107 Rayburn House Office Building
Washington, DC 20510

The Honorable Richard Burr
Ranking Member
Senate HELP Committee
455 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Cathy McMorris Rodgers
Ranking Member
House Energy & Commerce Committee
2185 Rayburn House Office Building
Washington, DC 20510

Dear Chair Murray and Ranking Member Burr and Chairman Pallone and Ranking Member McMorris Rodgers,

We, the undersigned patient organizations and related stakeholders, are writing to express our support for the Speeding Therapy Access Today (STAT) Act, H.R. 1730 and S. 670. The STAT Act is bipartisan legislation led by Representatives Gus Bilirakis (R-FL) and G.K. Butterfield (D-NC) and Senators Amy Klobuchar (D-MN) and Roger Wicker (R-MS) that aims to accelerate development of therapies across the spectrum of rare diseases and disorders and facilitate access to such therapies. Now more than ever, as Americans have seen the benefits of strong public health policy and targeted federal investments in medical and scientific innovation, we urge Congress to use this momentum to advance access to therapies for rare disease patients.

More than 30 million Americans live with one or more rare diseases yet between 93-95% of the over 7,000 known rare diseases have no approved treatments. When a product does successfully navigate the average 15+ year process that it takes to develop a rare disease treatment, patients often face unnecessary delays and barriers to access them. These delays result in avoidable deterioration in health and quality of life for members of the rare disease community.

The STAT Act builds on the passage of the 21st Century Cures Act and the successes of the first FDA Center of Excellence established for oncology products by adapting the model to address the unique challenges of developing treatments for rare diseases. The legislation proposes the creation of a Center

of Excellence (Intercenter Institute) for rare diseases and conditions that will serve as a cross-cutting, capacity-building, collaborative hub for rare disease activity at the FDA, supplementing but not supplanting any authorities of the existing Centers.

While interest in rare disease therapy development has increased since the passage of the historic Orphan Drug Act of 1983, the regulatory systems we have in place struggle to meet the unique challenges and complexities inherent in rare disease such as how to design, conduct and analyze clinical trials for small populations. The STAT Act's proposed Center of Excellence will ensure rare disease expertise is coordinated across the many FDA divisions reviewing rare disease products, and it will establish an effort to address the additional challenges in therapeutic development for communities affected by ultra-rare diseases.

The STAT Act also creates a Rare Disease Drug and Condition Advisory Committee to provide the FDA with community input and expert guidance on a wide range of rare disease issues, supporting the efforts of the Center of Excellence and providing guidance, when requested, to review divisions. This policy will expand FDA's existing community and patient engagement efforts, creating the first-ever federal advisory committee focused on rare diseases, something 16 states have instituted in recent years.

Finally, the STAT Act creates a voluntary third-party payor program to facilitate better communication and information sharing between the FDA, payors and the companies developing rare disease treatments. So many in the rare disease community face long coverage delays after a treatment is approved, and in some cases, patient access never materializes. The STAT Act seeks to ensure coverage policies reflect the totality of information used by the FDA to determine a drug's indicated use. The third-party payor program will leverage the experiences of similar efforts in the medical device space.

Rare disease is not just a health crisis, it is an economic one, too. The recently released National Economic Burden of Rare Disease Study found that the annual economic burden of rare disease reached nearly $1 trillion in the U.S. in 2019, including $418 billion in direct medical costs, $437 billion in productivity losses and $111 billion absorbed by families in uncovered medical and non-medical costs. Only 10% of these costs are attributed to treatments like prescription drugs and outpatient therapies, in part because so many rare disease patients have no approved treatments. This lack of condition-specific treatments instead leads to increased costs associated with hospitalization, outpatient care management, and productivity losses. Most of these expenses could be avoided with the development and access to treatments and cures.

Time is the most precious commodity for rare disease community. Each time a promising therapeutic target faces delays or demise due to the complexities in rare disease and strain on the existing regulatory infrastructure, lives are lost, investment is lost, and future scientific promise is unfulfilled.

Thank you for considering the needs of the rare disease patient community in the 117th Congress, and we look forward to working with you to advance impactful policies like the STAT Act. Should you have any questions about the STAT Act or the policy priorities of our community, please reach out to Jamie Sullivan with the EveryLife Foundation for Rare Diseases at jsullivan@everylifefoundation.org.

Sincerely,

ADNP Kids Research Foundation
Alexion Pharmaceuticals
Alliance for Patient Access
Alport Syndrome Foundation
American Behcet's Disease Association (ABDA)
Amicus Therapeutics
Amyloidosis Foundation
AnCan and Ann's Place/UsTOO Danbury PCa support
Angelman Syndrome Foundation
Argenx
Association for Creatine Deficiencies
Autoinflammatory Alliance
Avery's Hope
Barth Syndrome Foundation
Biogen
Born a Hero, Research Foundation
BRBN Alliance
CA Action Link for Rare Diseases (Cal Rare)
CARES Foundation
CDH International
CFC International
Chiesi Farmaceutical, Global Rare Diseases
Children's PKU Network / NPKUA
Choroideremia Research Foundation
Cure CMD
Cure GM1 Foundation
Cure HHT
Cure VCP Disease, Inc.
CureARS
CureDuchenne
CureSHANK
CureSPG50
Cyclic Vomiting Syndrome Association
Cystic Fibrosis Research Institute (CFRI)
Danny's Dose Alliance
Daphne's Lamp
EB Research Partnership
Endosalpingiosis Foundation Inc
EveryLife Foundation for Rare Diseases
Gaucher Community Alliance
Gene Giraffe Project
Genetic Alliance
Global Blood Therapeutics
Global Genes

Global Liver Institute
Harmony Biosciences
Haystack Project
HCU Network America
Hermansky-Pudlak Syndrome Network
Histiocytosis Association
Homology Medicines
Hunter Syndrome Foundation
HypoPara Support & Advocacy Inc
International Pemphigus Pemphigoid Foundation
International Waldenstrom's Macroglobulinemia Foundation
Jack McGovern Coats' Disease Foundation
KPM Group DC
Little Hercules Foundation
Little Miss Hannah Foundation
Littlest Tumor Foundation
Lowe Syndrome Association
Lymphangiomatosis & Gorham's Disease Alliance (LGDA)
MEPAN Foundation
Mission: Cure
MLD Foundation
MTM-CNM Family Connection
Myasthenia Gravis Foundation of America
Myositis Support and Understanding (MSU)
Narcolepsy Network
National Fragile X Foundation
National Leiomyosarcoma Foundation
National MPS Society
National Tay-Sachs & Allied Diseases Association (NTSAD)
NBIA Disorders Association
NTM Info & Research
Organic Acidemia Association
Orphazyme, US, Inc
Otsuka America Pharmaceutical
Ovid Therapeutics
Parent Project Muscular Dystrophy
People With Empathy
Phelan-McDermid Syndrome Foundation
Pheo Para Alliance
Phoenix Nest
Pompe Alliance
Prader-Willi Syndrome Association | USA
PXE International

Rare and Undiagnosed Network (RUN)
Rare Disease Innovations Institute, Inc.
Rare New England
RASopathies Network
Remember the Girls [a rare disease organization]
RSD Foundation
Sanofi Genzyme
SCID Angels for Life Foundation
Sick Cells
Siegel Rare Neuroimmune Association
Stronger Than Sarcoidosis
STXBP1 Foundation
Superficial Siderosis Research Alliance, Inc.
SynGAP Research Fund, 501(c)(3)
Texas Rare Alliance
The Assistance Fund
The E.WE Foundation
The Ehlers-Danlos Society
The Global Foundation for Peroxisomal Disorders
The Mast Cell Disease Society
The Oxalosis & Hyperoxaluria Foundation
The VHL Alliance
Travere Therapeutics
Treating CBS
Undiagnosed Disease Network Foundation
United Mitochondrial Disease Foundation
Usher Syndrome Coalition
VHL Alliance
Williams Syndrome Association
Wiskott Aldrich Foundation
Wylder Nation Foundation
Zambon USA Ltd.

CC:
The Honorable Nancy Pelosi
The Honorable Kevin McCarthy
The Honorable Chuck Schumer
The Honorable Mitch McConnell

Written Testimony of Dr. Paul A. Locke
Associate Professor
Johns Hopkins Bloomberg School of Public Health
Department of Environmental Health and Engineering
Baltimore, MD USA
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Submitted to the House Committee on Energy & Commerce, Subcommittee on Health hearing entitled, "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."
Thursday, March 17, 2022
10:30 AM EST
2123 Rayburn HOB – John D. Dingell Room – Hybrid Webex

Good morning Chairman Pallone and members of the Committee and Subcommittee. My name is Dr. Paul Locke and I am an Associate Professor at the Johns Hopkins Bloomberg School of Public Health in the Department of Environmental Health and Engineering. I am both an attorney and environmental health scientist, and am submitting testimony today in support of H.R. 5585, The Advanced Research Project Agency – Health Act or the ARPA-H Act, introduced by Representative Eshoo (D-CA). As you know, the ARPA-H Act creates a new agency (ARPA-H), which is charged with (1) fostering the development of new, breakthrough capabilities, technologies, and systems to accelerate innovations in health and medicine; (2) revolutionizing diagnosis, mitigation, prevention, and treatment of diseases through transformative health technologies and high-need cures; (3) promoting high-risk, high-reward innovation to develop high-need cures; and (4) insuring that the United States maintains global leadership in science and innovation and the highest quality of life and health for its citizens.

I fully support the establishment of ARPA-H and concur with the ambitious goals that this bill lays out. The ARPA-H is one of the most exciting – and important – initiatives put forth during this legislative session. ARPA-H is to be modeled after the similarly named Defense Advanced Research Projects Agency (DARPA), which has proven successful in accelerating ground-breaking, out-of-the box technologies for the military. An agency like ARPA-H is sorely needed. The SARS-CoV2 crisis brought to light the need for innovative approaches to medical and public health research. Because of urgency, commitment, and creative solutions, three successful vaccines were developed in less than a year. As conceived in this bill, ARPA-H has the potential to spark additional public health breakthroughs, especially for chronic diseases such as cancer, for which additional treatments and therapies are crucial.

To reach its full potential, ARPA-H must be established as an independent agency within the Department of Health and Human Services (DHHS). As an independent agency, it would be able to act autonomously when making decisions regarding research, funding, and the best ways to meet its goals. ARPA-H should be encouraged to collaborate with the National Institutes of Health, as the current version of the bill suggests. To some, the idea of incorporating ARPA-H into the NIH bureaucracy might seem reasonable. However, I believe that the approach set out

in H.R. 5585 is a superior way to reach the ambitious goals that this bill contains for at least three reasons.

First, as an independent agency within DHHS, ARPA-H would be able to act quickly when it comes to decisions regarding cutting edge research and the best ways to fund breakthrough advances. Technologies such as human chip models, cognitive computing technologies, 3D printing of living human tissues and organoids, and virtual humans offer great promise in helping scientists understand the diseases that afflict us and find treatments for them. Much of their promise lies in the fact that these methods are based on human biology, rather than the biology of other species. They can be developed and deployed rapidly to address emerging problems. For example, one new technology has already contributed to President Biden's goal of cutting the death rate of cancer by providing models that better describe the biology of cancer and can be used to develop more patient personalized anti-cancer therapy.[1]

Second, to be successful in fulfilling its mandate, ARPA-H needs to supplement the current biomedical ecosystem by identifying and filling neglected and underserved scientific areas to meet its goals and spark innovation.[2] While medical advancement has made great strides over the past decades, hundreds of thousands of Americans still die each year from diseases, such as cancer, that have been under study for the past five decades. President Richard Nixon launched the "war on cancer" more than 50 years ago with the passage of the National Cancer Act,[3] and now the Biden-Harris Administration has set the ambitious goal of reducing the cancer death rate by at least 50% within the next 25 years through a multi-front approach.[4] That is the visionary goal behind ARPA-H and expressed in the bill that Representative Eshoo has introduced.

Third, under the ARPA-H Act, this new agency will have the freedom to act independently to meet its goals while still coordinating with NIH to "ensure that the programs of ARPA-H build on and are informed by scientific research supported by the NIH."[5] Establishing ARPA-H outside of NIH distinguishes its individual goals from the larger mission of NIH which will allow the agency to completely devote its resources and decision-making authority towards transformational innovation.

In summary, I fully support H.R. 5585, The ARPA-H Act. As a public health professional who has studied and analyzed the legal and scientific issues surrounding how to improve biomedical science by adopting and encouraging human-centric methodologies, I recognize the important role ARPA-H and this bill could play in solving the health problems associated with chronic diseases. If structured as an independent agency within DHHS, ARPA-H will be a springboard

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[1] *See* Aaron Hudson, *Organ-Chips and Omics Advance Cancer Research,* GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Feb. 2, 2022); Han Fan, Utkan Demirici & Pu Chen, *Emerging organoid models: leaping forward in cancer research,* 142 J. HEMATOLOGY ONCOLOGY (2019).

[2] White House Office of Science and Technology Policy, *Advanced Research Project Agency for Health (ARPA-H): Concept Paper* (June 2021) (https://www.whitehouse.gov/wp-content/uploads/2021/06/ARPA-H-Concept-Paper.pdf).

[3] Gabrielle Emanuel, *50 years ago, Nixon gave the U.S. a 'Christmas present,' launching the war on cancer,* NPR (DEC. 23, 2021).

[4] Press Release, The White House, Fact Sheet: President Biden Reignites Cancer Moonshot to End Cancer as We Know It (Feb. 2, 2022), https://www.whitehouse.gov/briefing-room/statements-releases/2022/02/02/fact-sheet-president-biden-reignites-cancer-moonshot-to-end-cancer-as-we-know-it/.

[5] Advanced Research Project Agency-Health Act, H.R. 5585, 117th Cong. § 2 (c)(4)(E) (2021).

to a new way of conquering diseases that have so far eluded our public health and medical efforts.

Thank you for considering this testimony. The views expressed herein are my own, and do not necessarily reflect the official policy or position of the Johns Hopkins University or the Johns Hopkins Bloomberg School of Public Health.

Please feel free to contact me at plocke@jhu.edu if you need additional information.

Rep. Kevin McCarthy (CA-23)

Energy and Commerce Committee
Subcommittee on Health
March 17, 2022

THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

Mr. McCarthy. Chairwoman Eshoo, Ranking Member Guthrie, and members of the subcommittee, thank you for including the FORWARD Act (H.R. 5566), which I introduced last fall, in today's hearing.

Fungal Disease Prevalence

Fungal diseases pose a growing public health threat, particularly given limited rapid and accurate diagnostic tests, limited number of available therapies and vaccines, growing resistance to existing drugs, and rising prevalence rates. This includes the disease coccidioidomycosis, more commonly referred to as Valley Fever, which is caused by inhaling spores of the fungus *Coccidioides* largely found in the soil in the American Southwest, although it has now been found as far north as Washington State and can become life-threatening when it disseminates from the lungs throughout the body. According to the CDC's Morbidity and Mortality Weekly Report, Valley Fever incidence in California has increased significantly in recent years, increasing 213% from 2014 to 2018.[i] Another fungus - *Candida auris* - has now been identified in over 30 states and are becoming increasingly resistant to available antifungals, prompting the CDC in 2019 to list it as an urgent threat, the highest classification that "requires urgent and aggressive action."[ii] Further, COVID-19 has led to an increase in fungal infections because of the virus' effect on the immune system and because most treatments for COVID-19, like steroids, can weaken the body's defenses against fungal infections.[iii] Therefore, to better prepare for

future pandemics and to combat fungal diseases, policies, such as the FORWARD Act, are critical to spur the development of effective and next-generation antifungal drugs and biologics.

Fungal Disease Cost Burden

Fungal diseases range from minor superficial infections to systemic and life-threatening infections. Recent estimates suggest that fungal diseases cost the U.S. healthcare system more than $7.2 billion in 2017, a conservative estimate given many fungal diseases are underdiagnosed.[iv] For Valley Fever, some estimate the total lifetime cost burden of cases reported in 2017 in California to be just under $700 million.[v] In Arizona, total lifetime costs of 2019 cases is estimated to be nearly $736 million.[vi] Further, these costs are projected to rise with increasing prevalence, as the CDC reports the fungus that causes Valley Fever is now being found in the Pacific Northwest, including south-central Washington State. Kern County, California, which I represent, accounts for more than one-third of all reported Valley Fever cases statewide, or 2,786 of the 8,089 cases reported in the Golden State in 2021.[vii] Valley Fever and other fungal diseases pose a growing burden on our health care system, in part because of increasing prevalence, but also because diagnostics and treatments are limited.

Lack of Antifungal Drugs and Biologics

There are a limited number of treatments for most fungal diseases and development of antifungal drugs is particularly challenging. For Valley Fever, treatments are few, there is no cure, and there is no vaccine. Importantly, researchers recently successfully tested a Valley Fever vaccine for dogs, with two doses providing high levels of protection.[viii] There are three main available classes of antifungal drugs, compared to nine classes of antibiotics. The newest class of antifungal drugs, the echinocandins, were discovered in the 1970s and took nearly 30 years to be approved. In fact, only one antifungal drug (isavuconazole), has been approved and marketed in

the last decade for invasive fungal diseases.[ix] In contrast to antibiotic development, antifungal development is particularly challenging because fungal pathogens are closely related to humans as we are both eukaryotic organisms, making drug toxicity a key concern. Given the very limited number of antifungals in the pipeline, and with fungi becoming even more resistant to multiple classes of existing antifungals, the need for novel antifungal drugs and vaccines is increasingly important and the FORWARD Act would leverage existing government programs to help spur development. With the rising prevalence and cost burden associated with fungal diseases, along with the lack of available antifungal drugs and biologics, Congress has provided funding increases in recent years for the NIH and CDC to bolster scientific research and to enhance awareness of fungal diseases; however, the policy changes included in the FORWARD Act will be critical to build on these efforts in order to reduce the public health threat of fungal diseases.

The FORWARD Act

The Finding Orphan-disease Remedies With Antifungal Research and Development (FORWARD) Act (H.R. 5566) is designed to advance sustained efforts to combat fungal diseases in the short, medium, and long term. In the short term, the FORWARD Act would support basic research for fungal diseases; in the medium term, the bill would streamline FDA approval processes for new antifungal diagnostics, treatments, and vaccines; and in the long-= term, the FORWARD Act would incentivize and expedite the development of antifungal vaccines.

Specifically, the FORWARD Act would utilize existing government programs that serve as "push" and "pull" mechanisms to encourage antifungal development. Key provisions of the FORWARD Act include extending QIDP Designation for antifungal biologics, similar to Sec. 501 in the Senate's PREVENT Pandemics draft bill. Additionally, the FORWARD Act would

codify into law BARDA's successful CARB-X program and authorize the current spending level of $500 million to continue to support important preclinical antibiotic and antifungal research. Lastly, the bill would add Valley Fever to the FDA's PRV program, which serves to provide needed market incentives for the development of drugs for neglected diseases in which there is "no significant market in developed nations" and that "disproportionately impacts poor and marginalized populations."[x] In short, the FORWARD Act provides critical reforms needed to spur antifungal drug and vaccine development.

Conclusion

Fungal diseases like Valley Fever, along with antifungal resistance, pose a significant and growing public health threat. Further, the U.S. is not able to fully reap the benefit of its investment for effective COVID-19 therapeutics as these therapeutics can ultimately make some patients more susceptible to life-threatening and costly fungal infections. Antifungal drug and vaccine development is particularly challenging, and reforms are needed to spur novel antifungals development. The reforms included in the FORWARD Act serve to utilize existing government programs to bolster the antifungal and antibiotic development pipelines, which will be critical to enhance our ability to reduce public health threats from fungal diseases.

Again, thank you for including the FORWARD Act in today's subcommittee hearing.

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[i] Hurd-Kundeti G, Sondermeyer Cooksey GL, Jain S, Vugia DJ. Valley Fever (Coccidioidomycosis) Awareness — California, 2016–2017. MMWR Morb Mortal Wkly Rep 2020;69:1512–1516.
DOI: http://dx.doi.org/10.15585/mmwr.mm6942a2external icon

[ii] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

[iii] Shivakumar Narayanan, Joel V Chua, John W Baddley, Coronavirus Disease 2019–Associated Mucormycosis: Risk Factors and Mechanisms of Disease, *Clinical Infectious Diseases*, 2021; ciab726, https://doi.org/10.1093/cid/ciab726

[iv] Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of Direct Healthcare Costs of Fungal Diseases in the United States. Clin Infect Dis. 2019 May 17;68(11):1791-1797. doi: 10.1093/cid/ciy776. PMID: 30204844; PMCID: PMC6409199.

[v] Wilson L, Ting J, Lin H, Shah R, MacLean M, Peterson MW, Stockamp N, Libke R, Brown P. The Rise of Valley Fever: Prevalence and Cost Burden of Coccidioidomycosis Infection in California. Int J Environ Res Public Health. 2019 Mar 28;16(7):1113. doi: 10.3390/ijerph16071113. PMID: 30925716; PMCID: PMC6480346.

[vi] Grizzle AJ, Wilson L, Nix DE, Galgiani JN. Clinical and Economic Burden of Valley Fever in Arizona: An Incidence-Based Cost-of-Illness Analysis. Open Forum Infect Dis. 2020 Dec 28;8(2):ofaa623. doi: 10.1093/ofid/ofaa623. PMID: 33575419; PMCID: PMC7863867.

[vii] https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/CocciinCAProvisionalMonthlyReport.pdf

[viii] Lisa F. Shubitz, Edward J. Robb, Daniel A. Powell, Richard A. Bowen, Angela Bosco-Lauth, Airn Hartwig, Stephanie M. Porter, Hien Trinh, Hilary Moale, Helle Bielefeldt-Ohmann, James Hoskinson, Marc J. Orbach, Jeffrey A. Frelinger, John N. Galgiani,
Δcps1 vaccine protects dogs against experimentally induced coccidioidomycosis,
Vaccine, Volume 39, Issue 47, 2021, Pages 6894-6901, ISSN 0264-410X,
https://doi.org/10.1016/j.vaccine.2021.10.029.

[ix] Adriana M Rauseo, Ariella Coler-Reilly, Lindsey Larson, Andrej Spec, Hope on the Horizon: Novel Fungal Treatments in Development, *Open Forum Infectious Diseases*, Volume 7, Issue 2, February 2020, ofaa016, https://doi.org/10.1093/ofid/ofaa016

[x] (21 U.S.C. 360n)

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Written Testimony for the Record Submitted by
Gary K. Michelson, MD
Founder and Co-chair of Michelson Center for Public Policy
Before the Subcommittee on Health of the Committee on Energy and Commerce

The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

Thursday, March 17, 2022

To Chairwoman Eshoo, Ranking Member Guthrie, and Members of the Subcommittee:

On behalf of the Michelson Center for Public Policy, a 501(c)(4) social welfare organization that propels legislative change through meaningful collaboration with elected officials, government agencies, and civic leaders to achieve positive outcomes in education, equity, medical research, and animal welfare, I submit the following testimony in support of H.R. 2565, the FDA Modernization Act of 2021.

With strong bipartisan support, House leaders introduced the FDA Modernization Act of 2021 to revise a long-standing statute that limits preclinical studies to animal testing for new drugs. This follows action by the European Parliament in September to adopt a resolution—by a vote of 667 to 4—to phase out animal testing.

This is great news for public health as it marks a major milestone in transforming the biomedical sciences to embrace testing platforms that are more innovative and could be more relevant to human health than the standard animal testing platforms. The public expects the FDA and pharmaceutical companies to deploy first-rate science to develop and approve treatments for millions of Americans suffering from diseases. However, the current statute limits drug developers into antiquated methods that drive up costs, delay treatments, leave the afflicted without life-saving therapies, and churn through animals used in testing.

We are in desperate need of a reboot when it comes to drug development.

An outdated approach

Since its enactment in 1938, the Federal Food Drug and Cosmetics Act (FFDCA) has required data for safety and efficacy from animal tests for all new drugs and vaccines. But this 80-year-old statute has not caught up with the science.

Over the past several decades technology advancements have provided new nonclinical testing methods that have proven to be more effective in predicting the safety and effectiveness of drugs and vaccines for humans for certain disease areas. There are also several instances where we know animals testing is a poor method for predicting safety and effectiveness. For

example, in 2003, Elan Pharmaceuticals was forced to terminate a Phase II trial when an investigational Alzheimer's vaccine was found to cause brain swelling in humans.[1] No significant adverse effects were detected in genetically modified mice or nonhuman primates. In another example from 2006, six volunteers who were injected with an immunomodulatory drug, TGN 1412, suffered severe adverse reactions resulting from a life-threatening cytokine storm that led to catastrophic systemic organ failure.[2] TGN 1412 was tested in mice, rabbits, rats, and nonhuman primates with no ill effects.[3] Even recently, the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee concluded that animal models are "problematic" in assessing the safety risks of gene therapies derived from adeno-associated virus (AAV) vectors.[4] There have been severe adverse events in AAV vector clinical trials, including acute liver failure and encephalopathy, in children.[5]

Time and again, drugs and vaccines that proved promising in animal tests failed when tried in humans. At least 172 drugs that showed promise in animals for the treatment of Alzheimer's disease failed in humans,[6] as did 150 drugs tested successfully in animals for inflammatory diseases.[7] More than 114 therapies for stroke tested in animals failed in human trials.[8] More than 700 human trials of potential HIV/AIDS vaccines have been conducted, all of which gave encouraging results in animals, including monkeys and chimpanzees.[9] Yet not one has worked in humans.

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[1] Lemere CA. Developing novel immunogens for a safe and effective Alzheimer's disease vaccine. *Prog. Brain Res.* 2009; 175: 83–93.

[2] Allen A. Of Mice or Men: The Problems with Animal Testing. *Slate*. Published June 1, 2006.

[3] Attarwala H. TGN1412: From Discovery to Disaster. J. Young Pharm. 2010; 2(3): 332–336.

[4] Eglovitch JS. Animal models have limitations for safety assessment of gene therapies: FDA adcomm. Regulatory Affairs Professionals Society. Published September 2, 2021.

[5] George LA. Systemic AAV: Clinical Findings of Hepatotoxicty. Presentation at: CTGTAC: Toxicity Risks of AAV Vectors for Gene Therapy. September 2–3, 2021.

[6] Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development in Alzheimer's disease: An appraisal from 1984 to 2014. *J. Int. Med*. 2014; 275: 251–283.

[7] Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. USA* 2013; 110: 3507–3512.

[8] O'Collins VE, Macleod MR, Donnan GA, et al. 1,026 experimental treatments in acute stroke. *Ann. Neurol.* 2006; 59(3): 467–477.

[9] Bailey J. Letter. *Altern. Lab. Anim*. 2017; 45(4): 213–218.

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The FDA Modernization Act of 2021 would lift the requirement for animal testing and provide the FDA the opportunity to authorize the best testing methods, whether animal or non-animal, to determine the safety and efficacy of a new drug.

We must also consider the drugs and vaccines that did not work in animals that may prove to be effective in other nonclinical methods. For example, cyclosporine, a drug widely and successfully used to treat autoimmune disorders and prevent organ transplant rejection, was delayed because of animal tests.[10] How many potential cures were thrown out due to relying only on animal testing?

New methods

Bioprinted organ models, organ-on-a-chip models, "virtual humans," and artificial intelligence applications have been developed to predict human responses to new drugs more accurately and quickly. The benefit of these methods is that they are based on human biology. Recognizing the need for better models for human diseases, the Biomedical Advanced Research and Development Authority issued awards in September for human vaccine organ-chips[11] and lung-chips[12] for COVID-19 research.

Despite these signs of progress, the FDA continues to operate within the parameters of this outdated statute, compelling researchers to rely on animal testing, when evaluating new drug submissions.

Whatever role animal testing may have played in the past, we know that there are now new advanced methods to predict the safety and effectiveness of drugs and vaccines for humans.

Fortunately, Democrats and Republicans have joined together to push the FDA Modernization Act 2021 would lift the requirement for animal testing and provide the FDA the opportunity to authorize the best testing methods, whether animal or non-animal, to determine the safety and efficacy of a new drug. This measure will enable greater innovation in biomedical research and allow for the use of methods that are more likely to predict human outcomes.

A call to action

As physicians, we know that people come to medical professionals desperate for life-saving treatments. During the COVID-19 crisis, we as a nation realized that a protracted, bureaucratic,

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[10] Greek R, Greek J. Animal research and human disease. *JAMA* 2000; 283: 743–744.

[11] Walrath R. Draper inks $719K BARDA contract to develop lung chip for Covid-19 research. *Boston Business Journal*. Published September 23, 2021.

[12] Marx U, Andersson TB, Bahinski A, et al. Biology-inspired microphysiological system approaches to solve the prediction dilemma of substance testing. *Altern. Anim. Exp*. 2016; 33(3): 272–321.

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and inaccurate drug and vaccine approval process must be revamped. Thus, government and scientists brought urgency to the pandemic response, cut through organizational red tape, and developed successful vaccines in less than a year. We must bring this commitment and innovation to other drug development programs and get cures and treatments to those who desperately need them.

The FDA Modernization Act 2021 will free the FDA to allow for the best science to address the diseases that afflict us. This is an essential reform, and Congress and the Biden administration should pursue it with the same urgency they are bringing to the fight against COVID-19.

National Brain Tumor Society

DATE: March 16, 2022

TO: The Honorable Anna Eshoo, Chairwoman
The Honorable Brett Guthrie, Ranking Member
U.S. House Energy and Commerce Committee Subcommittee on Health

FROM: David Arons, Chief Executive Officer
Danielle Leach, Chief of Community and Government Relations
The National Brain Tumor Society

National Brain Tumor Society submits the following statement for the March 17, 2022, U.S. House Energy and Commerce Committee Subcommittee on Health hearing, "*The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight.*" We respectfully request that this statement be entered into the hearing record.

The National Brain Tumor Society (NBTS) is the largest patient advocacy organization in the United States committed to curing brain tumors and improving the lives of brain tumor patients and their families. Our vision of conquering and curing brain tumors is powered by our partnerships across science, health care, policy, and the business, nonprofit, and governmental sectors. We fund treatment-focused research and convene those most critical to curing brain tumors once and for all.

We support the Committee's work to bring attention to the proposed legislation in the hearing and are pleased that H.R. 5585, the *Advanced Research Project Agency-Health Act* and H.R. 6000, the *Cures 2.0 Act* will be two of the main focuses. NBTS is supportive of both H.R. 5585, the *Advanced Research Project Agency-Health Act* and H.R. 6000, the *Cures 2.0 Act* and hopes that they will be passed expeditiously in order to create the cures and quality of life improvements our brain tumor community urgently needs.

Why brain tumor patients and loved ones need breakthroughs now

Today, an estimated 700,000 people in the United States live with a primary brain tumor. More than 88,000 new diagnoses are expected in 2022, and as many as 170,000 additional cases of metastatic brain cancer are further anticipated. A diagnosis comes with a severe impact to patients and loved ones, and certain brain tumors are among the most life-threatening forms of cancer. Brain tumor patients and loved ones need breakthroughs now.

- **For those with cancerous brain tumors, few treatment options are available.** In addition to surgery and radiation, only five drugs and one medical device have been approved for malignant brain tumors since the 1980s. None of these are curative or extend survival more than two years on average. Survival rates for adult and pediatric brain tumor patients have not changed significantly over the past 30 years despite major

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breakthroughs made in the treatment of other cancers.

- **For malignant brain tumors, incidence and survival rates have remained stagnant for 45 years**, with five-year relative survival rate of 35.6% and only 6.8% for glioblastoma.

- **Tragically, pediatric brain tumors are the leading cause of cancer-related death among children and young adults ages 19 and younger**. There is currently no standard of care for treating some of the most aggressive pediatric brain tumors, and there has never been a drug developed and approved uniquely for these patients.

ARPA-H Principles

We believe ARPA-H holds the potential to confront specific challenges that, if solved, can substantially increase the likelihood of realizing transformative new treatments for brain tumor patients. We hope that ARPA-H has the following principles:

1. **Transformation** - All projects funded should aim to enable clear change in disease from that which is recalcitrant to manageable and curable.
2. **Convergence** - We encourage ARPA-H to foster greater opportunities and conditions for the disciplines of biology, engineering, physics, data mining and management, mathematics, psychology, and others to come together in new and robust ways.
3. **Risk-taking** - We urge that ARPA-H create the conditions for projects to be daring while still using strong scientific methods.
4. **Inclusive** - We know firsthand how critical the patient and caregiver experience can be to improving the quality of research. We urge ARPA-H to build in the role of patients, caregivers, and patient advocates from day one and leverage growing knowledge of race, ethnicity, sex, and economic status in research projects.
5. **Results-oriented** - Failure of experiments and projects is inevitable and expected in science. We urge ARPA-H to choose initiatives (including those we propose below) and see them through to completion, engaging parallel and sequential projects as needed to accomplish the end result in service of the "lasting revolutionary change" that is stated in DARPA's mission.
6. **Collaborative** - It is critical that strong federal cross-departmental collaboration and coordination occurs to ensure the success of this program. Cross-agency collaboration is critical to foster new initiatives and leverage existing projects and research to ensure smart investments of ARPA-H.

Why brain tumors are a perfect focal point for the new ARPA-H

Brain tumors offer a strategically advantageous place to start new initiatives in the following areas, as they also have the potential to yield significant progress for other disease areas.

Blood-brain barrier penetration - The blood-brain barrier's protective network has thwarted

many successful drug development and delivery attempts in neuro-oncology and other neurological indications over the years, yet the last five years have seen some innovation in this area. A coordinated, focused initiative is now needed to harness the powers of biology, engineering, and other technologies to develop novel platforms that enhance the delivery of targeted agents into the central nervous system.

Imaging and companion diagnostics - Brain tumor patients live from MRI to MRI constantly wondering if their imaging is telling them the truth about the status of their cancer. Yet, neuro-oncologists and neuro-radiologists remain frustrated about the ability to interpret MR images of brain tumors across scans as they try to decipher pseudo- progression from actual tumor growth. Advanced imaging, including metabolic imaging, remains fantastically expensive and is also hampered by its own unresolved issues such as distinguishing true tumor progress from an inflammatory response when immunotherapy is being administered. ARPA-H could make a transformative difference for brain tumor and patients with other diseases if it could bring together the best of medical academic imaging, industry, and the NCI's Cancer Imaging Program to solve these challenges with clear objectives to develop new imaging endpoints and companion diagnostics that can be used in drug and device clinical trials.

Innovation in biopsy - It is more important than ever for brain tumors and other brain diseases that novel biopsy approaches be developed, validated, and brought to scale, as repeat surgical biopsies of brain tumors is often not feasible. Emerging liquid biopsy approaches, including using cerebral spinal fluid, blood, and plasma are emerging, but there needs to be a concerted, focused, and coordinated effort to validate accurate, repeatable, and affordable liquid biopsies for patients with brain-related diseases.

Leverage the power of patient experience through technology - The rise of Real World Evidence as a potential source of data in prospective FDA-regulated clinical trials is also creating new opportunities for remote monitoring of patients through the use of wearable and other mobile technology. ARPA-H, based on experience from technology innovation from DARPA, could propel this field forward through a focused initiative on producing affordable, regulatory-grade, standardized patient- and caregiver-reported (symptom, sign, function) assessment tools. Validation and adoption of patient-reported outcomes measures would significantly improve the patient-centeredness of drug development and also help reveal clinical benefit in addition to survival.

Tumor heterogeneity - Glioblastoma and many additional adult and pediatric gliomas, as well as embryonal tumors like medulloblastoma, represent some of most cellularly heterogeneous cancers. To elucidate commonalities that can serve as actionable treatment targets amidst this inter- and intra-tumoral heterogeneity, research will benefit greatly from efforts that combine such emerging technologies and techniques as single- cell RNA sequencing and computational modeling powered by AI and machine-learning. Convergence with existing NCI-funded efforts like Project HOPE and GBM CARE offer immediate possibilities. Given the heterogeneity of glioblastoma and other brain tumors, if this level of biological diversity can be confronted and turned into biomarkers and treatment development pathways, it may provide significant benefits

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for less complex cancers.

Other Cures 2.0 provisions that will help to create cures and quality of life for brain tumor patients

Clinical trials education and diversity in clinical trials: Cures 2.0 includes a number of provisions designed to increase diversity in clinical trials, which are one of the best ways for brain tumor patients to receive potentially impactful new treatments during the course of their care. In Section 203: Increasing Diversity in Clinical Trials under (c), we encourage that you expand the role of the CDC's comprehensive cancer control program to add public education about clinical trials on an on-going basis in addition to the campaign called for in (c) (1). We applaud the inclusion of the GAO Study on barriers to improving diversity and reducing barriers to under represented groups in clinical trials and the authorization of funding for public awareness campaigns related to clinical trials. Our brain tumor community can have unique disability and accessibility issues that we propose any educational efforts to include as the programs are designed. In the taskforce proposed for making Clinicaltrials.gov more patient friendly, we strongly encourage the inclusion of patient advocacy organizations, in addition to patients and caregivers, for membership on the taskforce, since these organizations are often the frontline providers of patient education and information. We also urge the Committee to provide clarity on how these task forces will be constructed to sustain transparency.

Telehealth and decentralization of clinical trials: Expanded telehealth eligibility has improved access to care for brain tumor patients by making it easier to manage the myriad medical appointments they have to attend during their care experience, and may help improve patient outcomes and lower health care costs. In addition, telehealth eligibility has helped create accessibility to clinical trials and ensured retention in trials, which are critical to quality care for brain tumor patients. In Section 310, the incentives for decentralized clinical trials, again, we strongly encourage patient advocacy organization participation in the taskforce, since they not only educate and support patients during their treatment experience, but also often fund trials. This collaborative approach to provide incentives for decentralization for both public and private funding is crucial to the success of any effort.

Novel Trial Designs and Other Innovations in Drug Development: Clinical trial design in oncology and in particular, neuro-oncology has innovated to include adaptive designs using Bayesian statistics. We encourage the Committee's direction to foster use of this and other designs to expand opportunities for biomarker driven clinical trials that improve the potential to evaluate promising treatments in molecularly defined cohorts. In addition, we urge the Committee to in turn require the Food and Drug Administration to provide clarity regarding the use of historical data, real world data and other sources as it finds appropriate in the design of clinical trials. Specifically we ask that the Committee encourage the FDA to issue guidance related to the construction of external or synthetic control arms in oncology clinical trials.

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Patient Experience Data/RWE: We ask that under 304(a)(2) Considerations, that the guidance considers patient benefit risk assessment and in particular the needs of recalcitrant cancer patients.

Education for Caregivers: Caregivers are a crucial partner in the care of brain tumor patients. In Section 201: Educational Programs and Training for Caregivers under (b), we ask that you include emotional health and psychosocial among the types of programs and training funded by HHS.

We look forward to working together, and if you have any questions or would like additional information, please contact Danielle Leach, Chief of Community and Government Relations, at dleach@braintumor.org.

Obatala

Testimony of
Trivia Frazier, PhD, MBA, CEO Obatala Sciences
Before the Subcommittee on Health of the Committee on Energy and Commerce
Thursday, March 17, 2022
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

On behalf of Obatala Sciences, a New Orleans biotech company that offers research enabling products and brain power to scientists in industry and academia with the goal of advancing tissue engineering and regenerative medicine, I offer this testimony in support of the FDA Modernization Act of 2021 (H.R. 2565 and S. 2952).

This legislation is critical, as it broadens the scope of acceptable nonclinical models for drug development, and enables researchers to test a drug's safety and efficacy using more advanced and humane methods in place of animal testing where possible. Such an amendment, if enacted, could pave the way for faster, more effective, and more humane therapeutic development.

When the FFDCA was enacted in 1938, animal models seemed like the best way for drug developers to study how therapeutics might act within a biological setting. In theory, then, animal testing should ensure that only the safest, most effective drugs make it to clinical trials. Over the years, innovation has changed the equation, and better models are now available in many cases. Innovation in the years ahead will almost certainly produce superior methods than animal testing in nearly all cases.

Under the current regulatory scheme:

- 90 to 95 percent of drugs found safe in traditional nonclinical tests fail during human clinical trials due to toxicities not predicted by traditional animal tests or because of lack of efficacy, in large part, because animal data are not predictive of the human response.
- It takes from 10 to 15 years to develop a new drug, costing between $1 to $6 billion.
- Estimates suggest that, relative to *in vitro* models, animal testing is 1.5- to 30-times more expensive.

We can apply human biology-based test methods to better predict how humans will respond to drugs in clinical trials. We are already on the verge of the next phase of modern drug development and promoting the exclusive use of data from animal models doesn't reflect 21st Century scientific advancement. H.R. 2565 and S. 2952 will be catalysts for this transition to modern science. We welcome the opportunity to address any concerns regarding our support of

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this monumental legislation, and we are hopeful that you will consider the collective voice of our community in support of moving it forward.

Sincerely,

Trivia Frazier, PhD, MBA
President and CEO
Obatala Sciences, Inc.

March 16, 2022

The Honorable Frank Pallone
2107 Rayburn House Office Building
U.S. House of Representatives
Washington, DC 20510

The Honorable Cathy McMorris Rogers
1035 Longworth House Office Building
U.S. House of Representatives
Washington, DC 20510

Dear Chairman Pallone and Ranking Member Cathy McMorris Rodgers,

On behalf of the Personal Care Products Council (PCPC), the voice and advocate for 600 member companies representing the $499.6 billion global cosmetics and personal care products industry, The Humane Society of the United States (HSUS), the nation's most effective animal protection organization, and the Humane Society Legislative Fund (HSLF), the separate lobbying affiliate of HSUS, we urge this subcommittee, and the broader Energy and Commerce committee, to consider including H.R. 6207, the Humane Cosmetics Act of 2021, in any moving legislative packages. The Humane Cosmetics Act ends new animal testing for cosmetics but gives FDA the discretion to require new testing if necessary.

Our organizations have long advocated for government recognition and acceptance of alternative testing methods. If enacted, this legislation would require the FDA to establish a strategic plan for developing and approving non-animal testing methods and strategies. The Humane Cosmetics Act of 2021 would also prohibit new animal testing of cosmetics and their ingredients as well as prohibit the sale of cosmetics in the United States that have been tested on animals. We stand firm in our shared goal to eliminate new cosmetic animal testing and promote recognition and acceptance of non-animal approaches to cosmetic safety assessments and we support enactment of this vital legislation.

Thank you for your support and we look forward to working with your Committee on advancing H.R. 6207, the Humane Cosmetics Act of 2021.

Sincerely,

Mallika Vastare
Vice President, Government Affairs
Personal Care Products Council

Tracie Letterman
Vice President of Federal Affairs
Humane Society Legislative Fund

Katie Conlee
Vice President of Animal Research Issues
The Humane Society of the United States

Perspectum

STATEMENT FOR THE RECORD

Submitted by
Rajarshi Banerjee, M.D. , Ph.D., MSc., MRCP
Chief Executive Officer, Perspectum

"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
Hearing before the Subcommittee on Health
Committee on Energy and Commerce
March 17, 2022

Chair Eshoo, Ranking Member Guthrie, Chairman Pallone and Ranking Member McMorris-Rodgers:

Thank you for the continued opportunity to discuss with the Subcommittee Perspectum's views on the need and opportunities arising from the United States' commitment to modernizing biomedical research infrastructure to keep pace with the astounding and rapid developments which are occurring almost daily in science. As a scientist, medical doctor, and co-founder of a diagnostics company, Perspectum, I commend you for continuing to move forward on this package of bills which collectively attempt to bolster biomedical innovation in the United States and improve oversight of public health programs,

This will come as no surprise given our discussions with many of you, but I welcome the opportunity to urge that the Subcommittee devote substantial attention to examination of how research can improve the diagnosis, treatment and potentially even curative treatments for long-COVID-19, or as some call it, "long-COVID," or Post-Acute Sequalae of SARS-CoV-2 infection ("PASC").

While infection rates are declining for the Omicron variant of COVID-19, unfortunately we still see concerning reports about the lingering effects of this virus. It is important to recognize that long-COVID may have a substantial effect on public health for years to come, potentially leading to significant disability. Quite simply, we need to be prepared.

As a current reminder, I would like to submit for the record a Reuters article from March 4th in which a pre-Omicron Danish study of 152,000 people found that almost a third of those who tested positive for COVID-19 reported symptoms that linger between six and 12 months after diagnosis. This is a recent and compelling reminder of the potency of long-COVID.

https://www.reuters.com/business/healthcare-pharmaceuticals/almost-third-people-report-lingering-symptom-6-12-months-after-covid-19-study-2022-03-04/

At the outset of this hearing, I hasten to recognise Oversight Subcommittee Chair Diana DeGette and former Chair Fred Upton for their vision, foresight and determination in drafting

and advancing the CURES 2.0 legislation. Your hearing today, and that there are at last count 91 cosponsors of H.R. 6000 speaks volumes about it, not only the need for this bill, but also the overwhelming support it is receiving in Congress.

Indeed, it is important to recognise the achievement of the predecessor law, and at Perspectum we hail the Committee's persistence and leadership in drafting, pushing to enactment, and then monitoring implementation of the landmark 21st Century Cures law (P.L. 114-255), which has done so much to spur innovation in health care research, treatment, and delivery. Your deep commitment to improving the lives of patients is evident by this substantial work, and it is even more impressive that you are now working on the follow-on, comprehensive, CURES 2.0 bill.

Today, I would like to provide the Subcommittee with the benefit of Perspectum's views on long-COVID, a family of diseases to which we have devoted considerable energy from the start of the pandemic. We are keenly aware, and are especially heartened, that the authors recognise the importance of advancing knowledge of long-COVID by addressing it in the first section of the bill. It is my hope this legislation can be enacted this year and I offer my continued assistance to members and staff whenever needed.

Who We Are:

A brief mention about my background may help you put my remarks in context. I studied medicine at Oxford, and became interested in acquired heart and liver disease, which were alarmingly on the rise driven by obesity and alcohol use, conditions which are unfortunately all too present in the United States as well. I realized that I wanted to play a role in improving care for these patients and focused on developing customized solutions to deliver better outcomes to promote what we call in Britain, "kinder healthcare." This led me to build a medical technology company, assemble a highly capable multidisciplinary team with many great diagnostic scientists, engineers and clinicians, and direct our focus to work on these challenges, starting first with liver disease.

Perspectum now is a leading commercial-stage, precision health company based in the United Kingdom with offices in the United States. Our approach to patient care draws on the expertise of the renowned physicians and scientists who lead our company, and we collaborate with world-leading experts on metabolic diseases, cancer, diabetes and other chronic diseases to push forward research. In offering advanced diagnostic solutions to doctors, we can support better decision-making, personalized care for patients, and better outcomes.

At Perspectum, we are very proud of our flagship product, LiverMultiScan, which has been cleared by the Food and Drug Administration for the non-invasive assessment and monitoring of liver disorders that may include nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), a severe form of fatty liver disease. LiverMultiScan is now being used in over 250 sites in the US, and is part of the Medicare and AIM pathways for the safer evaluation of liver disease, replacing liver biopsy. We have other FDA-approved products,

including those to support precision surgical decision-making for hepatologists and provide clinicians with highly-specific tools to monitor biliary diseases, such as primary sclerosing cholangitis (PSC).

As a company, Perspectum is committed to innovation and matters of public health and healthcare.

Our Response to the Emerging Covid-19 Pandemic:

The long-term impacts of COVID outside the lungs were not known in the period of March-April, 2020 when COVID first was discovered and then declared a pandemic. Perspectum already had many great medical innovation and clinical scientists, so it was only natural to focus our energies on COVID-19.

We undertook the world's largest study of mapping organ health in 'post-COVID' individuals. We enabled existing mobile MRI scanners on site at our main office with our advanced software services to look at multiple organs in the torso, using a single 30-minute scan to find out if a patient has sustained organ damage by a disease. We became the first to show that organ damage can occur in COVID patients even if they have not been hospitalized. Our preliminary figures indicated that, four to five months after infection, almost 70 percent of COVID patients with persistent symptoms had sustained damage to one organ, and a quarter of these have two or more organs damaged (Dennis et al. 2021, referenced below).

Compelled by findings of our recently published community-based clinical study (designed and conducted by a Perspectum team in Oxford and our collaborators entitled, "Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study," Dennis et al. (2021). BMJ Open, 11(3), e048391[1]), we are continuing to explore the possibility that there are unique health issues facing women presenting with Long-COVID. Of the individuals in our community study, 71% were females and 19% had been hospitalized with COVID-19. Impairment in the liver, heart or lungs was associated with further organ impairment in 63%, 62% and 48% of individuals, respectively. I also currently serve as a team member of the largest clinical long-COVID study to-date called STIMULATE-ICP2 (Symptoms, Trajectory, Inequalities and Management: Understanding Long-COVID to Address and TransformExisting Integrated Care Pathways), led by University College London Hospitals NHS Trust and University College London. The 2-year study is designed to deliver the needed knowledge to scientists and clinicians to improve patient care and to inform policymakers, while collecting real-world data at scale.

Real-Time Revelations:

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[1] https://bmjopen.bmj.com/content/11/3/e048391

2 https://www.stimulate-icp.org/

The long-COVID communities of researchers, clinicians and patients are extremely gratified that Congress had the wisdom to provide $1.15 billion in funding to the National Institutes of Health for grants which will begin to answer the myriad mysteries of PASC, including whom it affects, for how long, and how they should best be treated.

From our work, we become more and more convinced about the need to devote additional resources to long-COVID – to help patients, to identify how best to treat the range of illnesses long-COVID embraces, and to determine the extent and duration of post-COVID illness, among many issues. Even now in our third-year of the pandemic and despite the best efforts of researchers and clinical medical experts, we still have not identified sound clinical treatment pathways for long-COVID patients, do not understand whom it affects and for how long, and are still addressing the PASC crisis in "real-time," while many people are also now dealing with the after effects of COVID-19 infections persisting.

As you may recall, as CEO, I submitted testimony to the April 28, 2021, Health and the Environment Subcommittee hearing on Long-COVID in which Perspectum observed five key points that must be considered in any on-going study of long-COVID:

1) In the majority of persons whose COVID does not resolve in three months, there can be significant organ damage which should be recognised early;
2) Long-COVID is a multi-system illness that must be treated holistically;
3) We have no idea how long it will persist in a patient, and this could engender a whole new cohort of the disabled, especially among healthcare workers;
4) We are beginning to see signs that the health care delivery system cannot keep up with the need for patient treatment; and
5) More information needs to be developed about the disproportionate impact of long-Covid on certain patient populations, be it race, income, age, geography or pre-existing conditions, to name a few.

These observations largely remain true today and this supports the focus of the Committee's examination of how to speed work on emergent scientific challenges such as PASC.

For the benefit of the Committee, let me take this opportunity to share our thoughts on how the long-COVID sections of the CURES 2.0 proposal could be strengthened.

Comments on Sec. 101, "Further Understanding the Implications of long-COVID":

We are enormously appreciative of the prominent and early long-COVID language included in the CURES 2.0 bill; it is to be noted that the authors obviously understand the importance of work to help patients in this area because you included as the very first section,

Sec. 101, language on the "Further Understanding the Implications of Long-COVID." It is that language on which we wish to make several recommendations as follows.

First, at the outset, we urge that efforts be undertaken to develop a common understanding of the definition of "long-COVID" – whether in this legislation or by some other administrative, congressional or other action. It is extremely hard to measure the extent of PASC or know how long to monitor its progression in patients as well as our success in addressing it, without a common understanding of what and how "long" long is. Understanding these things is of the utmost importance from the perspective of patients' physical and mental health. We note that the World Health Organization (WHO) recently published a clinical case definition of post-COVID. Although the WHO definition has been criticized by some as lacking, we concur with the motivation behind the WHO's action – that a lack of consensus on the time of onset and length of symptoms could impede our complete understanding of the extent and duration of PASC; this undoubtedly affects medical research and the utility of study results.

Other recommendations on the specific subsections of Sec. 101: "Further Understanding the Implications of Long-COVID":

General Comment: As a general comment on the purpose of Sec. 101, we believe that this is an important and certainly a necessary goal. We also appreciate that the implications of PASC are far from being identified totally. That said, we urge that the Committee move beyond "study" to action on long-COVID where possible and especially in clinical settings and care, as there are published data showing that patients with long-COVID are at higher risk of death, disability and rehospitalisation.

Perspectum respectfully suggests you have the opportunity to play a leadership role in strengthening the US government's response to long-COVID by broadening this language. For example, this could be accomplished by a sectional title change:

We suggest that the title embrace the notion of encouraging action on the range of issues associated with long-COVID, beyond the national coverage study. We recommend the Section 101 title read "Establishing a Framework for Priority Action on Long-COVID."

While there is substantial funding being devoted to long-COVID research, and more to come as funding for programs under the ARPA-H entity you authorize gets underway, even so there is need for us to act now where we can. The job is substantial, spanning all the public health agencies as well as the Social Security Administration and perhaps the Department of Labor (e.g., the Office of Disability Employment Policy and the Occupational Safety and Health Administration) and the Internal Revenue Service among others.

Authority for New Coordinating and Monitoring Bodies: For this reason, we respectfully request you consider establishing two coordinating and monitoring bodies. The first would be an inter-agency Task Force which will bring together all of the Federal

government's myriad agencies who address long-COVID. The second would be a new "Office of Long-COVID" established under the authority of the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS).

Virtually every public health agency is involved in PASC in some way, from the Centers for Disease Control and Prevention to the National Institutes of Health, but also agencies such as the Health Resources and Services Administration which we believe will play a growing role as the need for increased service delivery in this population becomes more evident.

Over the years, the ASH has played a leadership role in coordinating the government's response to health crises, for example with AIDS in the mid-1980s. So, this would be a natural home for such an effort. That said, if you determine a broader need exists so that programs in human services could also be embraced, a new office could be established at secretarial level.

While we understand the natural reluctance to create bureaucratic entities, in this case there is an urgent need for such a coordinating body, which can both provoke action and monitor the range of results. Likewise, such a need exists across government agencies. If there are concerns about the length of operations of these offices, they could be term-limited with the possibility for reauthorisation in the future.

Sec. 101(a)

Regardless of who is the lead in Federal governmental long-COVID efforts, we think there is a need for further understanding the implications of a number of issues associated with long-COVID beyond what is in your draft legislation.
Sec. 101(a)(1)

Additional requirements for the study: For the Survey, authors may want to direct the Department of Health and Human Services to study current funding and sources for coverage of long-COVID in both the public and private sectors; this would complement the current language which surveys patients only. Further, we suggest you consider providing guidance on how "large" the national survey is – to make certain it adequately reflects a range of geographic areas, including rural and urban, a range of age groups, young to old, and a range of persons from varying socio-economic backgrounds, races, and genders. Health inequalities have been highlighted by COVID-19 and apply to long-COVID patients as well.

Additional topics for the study: We also recommend that the draft go beyond assessing the broad topics of health care coverage, long-term care coverage, and disability coverage to address problems more specifically with factors such as:

-Eligibility for coverage in these three areas:

- *for primary care visits*
- *access to diagnostics,*
- *follow-up with specialists, and*

- *on-going care and rehabilitation needs, including support to return to employment.*

-Eligibility for services based on issues such as lack of an initial positive COVID test (discussed much at the April 28 hearing); and,

-The need for a standardized definition of disability to ensure quick access to disability coverage.

Sec. 101(a)(2)

Survey Report: We agree it is important for Congress to have an expedited report about the coverage survey; that said, it might be helpful to require that in writing, in the report, that the Secretary or his designee provide a description of who was surveyed when and where, and a discussion of the answers to the above questions we suggested you pose.

Sec. 101(b)(1)

Learning Collaborative: Page 4, lines 1-2, you may want to make clear that the representatives should be from key sectors of the health care community "who have expertise in long-COVID."

Sec. 101 (c)

COVID Scientific Research for Children: We heartily endorse the addition to the proposal of this authorization for NIH grants to research the long-term effects and treatments of COVID-19 in children. We are starting to engage in such research in the UK and welcome any future collaboration.

Sec. 101 (d)

Study on Disparities in Long-COVID: Additionally, we welcome this addition to the previous draft, which will authorize a National Academy of Medicine study on disparities in racial and ethnic minority groups on the diagnosis of, severity of symptoms, access to care, and treatment for long-COVID. As the pandemic progresses, we are finding such disparities more and more, and their identification can only improve diagnosis and treatment outcomes.

Sec. 101 (e)

Education and Dissemination of Information with Respect to Long-term Symptoms of COVID-19: As previously cited, we are concerned about the relative lack of attention given to managing long-COVID clinically, and therefore a public education program at HHS is very welcome. Likewise, dissemination of information to providers under this program is a welcome

addition to the bill, although we caution any such program must not only be flexible enough to provide information in as close to "real-time" as possible. The information dissemination must also embrace the full range of issues associated with PASC, including appropriate diagnostic tools and treatment options.

Funding for Programs Authorized in Sec.101: We are heartened that H.R. 6000 has now allocated specific authorizations for programs contained in this section, in contrast to the "such sums" authorization in the previous draft. This is an improvement. Additionally, we note the relative lack of public discussion and thus priority devoted to long-COVID compared with COVID itself. As we watch the real possibility that this pandemic will become endemic, there is not enough focus on the fact that long-COVID most certainly could linger.

By-Pass Budget: As you know, the National Cancer Act of 1970 provided a special authority that allows the National Cancer Institute to submit a "bypass" budget directly to The White House without Department review. The intent was to make certain that cancer research received what the scientific community felt was necessary, unimpeded by more political considerations. Given the importance of continuing PASC research, we suggest you might consider authorizing the HHS to submit a "bypass budget" for some or all of the long-COVID programs authorized in H.R. 6000. If there are concerns about this precedent, it could be time-limited.

Potential Addition to Sec. 101:

NIH Report: Given that the majority of long-COVID activities are currently taking place at the National Institutes of Health, and recognizing the large appropriation for those activities Congress provided to NIH, a good idea may be to consider requesting a brief-but-comprehensive biannual report (or some other patient-friendly medium) from the agency on its COVID research activities. While we would not want to divert NIH's work, it is important that the patients know what research is being undertaken and where should patients and their families wish to participate or learn more. Clinicaltrials.gov may be too specific and not easily navigable for these purposes.

ARPA-H

Let me also take this opportunity to commend you, Chair Eshoo, for your foresight in drafting H.R. 5585, the "Advanced Research Project Agency-Health Act," which also enjoys solid support with 57 cosponsors. I can think of no greater way to enhance the successes we are achieving in biomedical research and health care delivery than to incentivize projects that will transform medicine for the benefit of patients. The prospect of devoting considerable resources to high-risk, high-reward projects is exciting to medical researchers.

Conclusion:

In closing, Madame Chair and members of the Subcommittee, we at Perspectum commend your foresight in addressing our Nation's over-arching biomedical research

infrastructure, and in specific the public health problem that is long-COVID. From our work over the past two years, it is clear that there is much to be learned about PASC, but we must ensure doctors and other health care providers recognise and diagnose long-COVID early in a patient's illness. We also must develop clear clinical guidelines while simultaneously developing effective treatment pathways. I am outlining just a few of the many challenges our health care delivery systems face – and I fear we are losing precious time for many patients and their loved ones already. It is my hope that the benefit of our experience will help direct you as you move forward, and I remain available to provide the benefit of our expertise to you at any time.

Thank you for this hearing, and thank you for the opportunity to submit this testimony today.

PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
5100 Wisconsin Ave. NW, Suite 400 • Washington, DC 20016 • Tel: 202-686-2210 • Fax: 202-686-2216 • pcrm@pcrm.org

Statement for the Record

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

March 17, 2022

Submitted by: Kristie Sullivan, MPH, Vice President, Research Policy

On behalf of the Physicians Committee for Responsible Medicine, thank you for the opportunity to submit this statement for the record regarding the need for policy and program changes that integrate human-specific *in vitro* and computational methods in nonclinical drug safety and efficacy testing. Legislative efforts to improve the way drugs are developed and tested must compel FDA action to remove the requirements for animal experiments and expand FDA efforts to evaluate and accept human-specific approaches.

The Physicians Committee is a 501(c)(3) nonprofit organization supported by over 175,000 members nationwide working for effective, efficient, and ethical medical research and product testing. We collaborate with federal and state agencies, the private sector, and academia to improve public health and medical practice. We request this statement be included in the record for the Subcommittee on Health's March 17, 2022 hearing entitled "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

Fundamentally, human-specific approaches are more relevant to humans and predictive of human outcomes than traditional animal studies because they utilize human cells, tissues, and data, and even offer the ability to model diverse patient populations prior to clinical trials. Traditional nonclinical studies rely heavily on the biology of other animal species, frequently that of dogs, mice, rats, and non-human primates. Increasingly, scientists spanning various stakeholder groups, affiliations, and backgrounds, including the FDA and industry, acknowledge that these animal studies do not always provide accurate information for humans and that there is a need to integrate methods that are more predictive for humans. The 95% failure rate of investigational medicines moving from nonclinical to clinical studies indicates that we can do better to overcome translational challenges – for humans that need safe and effective medicines and for non-human animals who are used in testing.

FDA's Policies and Practices

The FDA's regulations and guidance play a key role in the continued use of animal studies over modern human-specific approaches because they require and recommend animal use. While human-specific methods have significantly advanced in recent years, and many are

commercialized, many FDA policies have not been updated to account for this progress. Currently, FDA policies include requirements and recommendations for the submission of data from animal tests, without providing flexibility for submission of data from human-specific approaches. Without certainty that new approaches will be accepted, companies will continue to submit data from traditional animal tests.

The code of federal regulations definition of 'nonclinical' should be amended to include *in vivo*, *in vitro,* and *in silico* approaches, rather than just *in vivo* and *in vitro*. The word 'nonclinical' should then be used throughout the regulatory text instead of inconsistent references to 'animal' or '*in vivo'* data. These regulatory changes would help to ensure that the best methods for predicting human outcomes are included in drug review, whether they include *in vivo* animal tests or not. In addition, many FDA guidance documents include language stating that alternative methods to the enumerated animal tests are accepted where appropriate. Unfortunately, many guidance documents also include a disclaimer that alternative methods may be used if they meet the requirements of applicable statutes and regulations, making the intended flexibility impractical until the regulations allow flexibility. Additionally, some FDA guidance contain conflicting recommendations for testing.

For these reasons, the Physicians Committee recommends that any effort to encourage innovation and improve drug development outcomes should require agency action to update regulations and guidance to explicitly communicate acceptance of human-specific nonanimal approaches.

Draft Legislative Text to Advance Human-Specific Methods:

TITLE VI--REAUTHORIZATIONS AND IMPROVEMENTS RELATED TO DRUGS

SEC. ___. Human-Specific Translational Models and Tools.

Regulations and Guidance for Nonclinical Laboratory Studies.

1) Regulations. – Not later than September 30, 2023, the Secretary, acting through the Commissioner of Food and Drugs, shall publish in the Federal Register notice of proposed rule changes, including—

> *A. Amendment to the definition of 'nonclinical' in 21 C.F.R. § 58.3(d) to include in vivo, in vitro, and in silico approaches;*
>
> *B. Amendments to regulations promulgated under 21 C.F.R. to employ 'nonclinical' in lieu of references to 'animal,' 'in vivo,' or 'in vitro' data.*

2) Guidance. – Not later than September 30, 2023, the Secretary shall conduct a review of existing guidance documents for nonclinical testing to—

> *A. Identify and amend guidance that recommend animal tests to explicitly communicate acceptance of alternative methods;*

B. Of the relevant guidance, identify which guidance contain conflicting recommendations and amend or delete to resolve inconsistencies;

3) Report. – Not later than September 30, 2024, the Secretary shall publish in the Federal Register the issuance, reissuance, modification, and/or deletion of regulations and guidance identified during the review under this section.

FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND)

To encourage innovation and improve drug development outcomes while reducing animal testing, PDUFA VII should fund qualification of human-specific nonanimal approaches via FDA's ISTAND program and include commitments from the FDA regarding deliverables.

In November 2020, the FDA launched the ISTAND pilot program, which created a much-needed path for the agency to consider and potentially accept new approaches through a scientific evaluation process called qualification. Once qualified through ISTAND, a method gains the FDA's stamp of approval for the qualified purpose, and all drug sponsors may confidently use the human-specific approach.

ISTAND is a broad program that also includes other drug development tools, so dedicated funds for qualifying human-specific approaches with deliverables would help ensure the agency prioritizes human-specific approaches.

For these reasons, the Physicians Committee recommends that PDUFA VII fund the FDA's ISTAND program, with dedicated funds allotted for qualification of human-specific approaches.

Draft Legislative Text to Advance Human-Specific Methods in PDUFA VII:

TITLE VI--REAUTHORIZATIONS AND IMPROVEMENTS RELATED TO DRUGS

SEC. ___. Human-Specific Translational Models and Tools.

Qualification of Drug Development Tools.

1) Funding for the Qualification of Human-Specific Approaches.– This Act designates $5,000,000 to be spent on activities to support the qualification of nonanimal approaches within the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program. ISTAND provides a pathway for regulatory acceptance of innovative human-specific methods that can better protect public health, improve the safety and efficacy of drug development, and reduce animal testing. Allocated funds should cover salaries for designated staff to qualify nonanimal methods through the ISTAND program, to update agency guidance to recommend qualified methods, and to train staff on qualified nonanimal approaches, in addition to other activities.

2) Report.– Not later than September 30, 2025, the Secretary shall publish in the Federal Register a report on activities related to the qualification of human-specific approaches through ISTAND, including eligibility criteria, a list of qualified methods, guidance changes

recommending the use of human-specific methods qualified through ISTAND, and information on agency training on qualified human-specific methods, in addition to other activities.

Delivering safer and more effective therapeutics requires agency and industry policies, practices, and programs to keep pace with scientific and technological advances. Human-specific approaches have the potential to transform nonclinical drug safety and efficacy testing by providing information specific to humans, allowing companies and the agency to make more informed decisions earlier in the drug development pipeline.

The Physicians Committee appreciates the Subcommittee's efforts to encourage innovation in medicine. Please do not hesitate to reach out with any questions.

March 17, 2022

The Honorable Frank Pallone
Chairman
Energy & Commerce Committee
2107 Rayburn HOB
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
Ranking Member
Energy & Commerce Committee
1035 Longworth HOB
Washington, DC 20515

Re: H.R. 7008 – The Pre-approval Information Exchange Act of 2022

Dear Chairman Pallone and Ranking Member McMorris Rodgers:

The undersigned organizations, representing a diverse coalition of stakeholders in American healthcare, write in support of the *Pre-approval Information Exchange Act of 2022* (H.R. 7008). This important bill will help speed patient access to new, potentially lifesaving, treatments by reducing the time between Food & Drug Administration (FDA) approval of a treatment and the beginning of coverage for that treatment.

Pre-approval information exchange (PIE) is the practice of drug and device manufacturers communicating certain truthful and non-misleading economic and clinical information to health payers regarding therapies or new indications of previously approved products in the FDA pipeline before they are approved. This allows payers to plan appropriately for the economic impact a new treatment will have before the beginning of the plan year in which approval is anticipated. The language includes provisions to ensure that information is provided only to appropriate audiences. The bill also empowers payers and manufacturers to begin developing purchasing agreements before approval, which can significantly reduce the amount of time between approval and patient access. This period between approval and coverage is sometimes referred to as the "Valley of Death."

FDA guidance initially drafted under Dr. Califf's leadership in 2016 and finalized in 2018 permitted PIE but did not clarify if manufacturers can proactively share this information or are limited to providing it in response to a payer request for information. As a result, many manufacturers are hesitant to engage in PIE, leading to preventable delays in access to new treatments.

Health care decision-makers find greater need for proactive PIE communication as the health care system evolves from a fee-for-service payment structure to a value-based model rewarding quality, improved patient outcomes, and cost-efficiency by facilitating more timely negotiations of value- and outcomes-based contracts. PIE is particularly important in fields with rapidly evolving therapeutic options, such as but not limited to oncology and the treatment of rare diseases. For example, many cancer treatments are approved only for one specific type of cancer but later found to be effective in treating other types as well. Cell and gene therapies, a growing class of treatments, are often used to treat rare diseases but have complex development processes and high list prices, sometimes ranging from hundreds of thousands of dollars to more than a million. Delays in patient access due to statutory barriers to timely exchange of information can have serious consequences. Publicly funded payers, like Medicare and Medicaid, have statutorily limited flexibility to change their prescription drug formularies

during a plan year, which can lead to beneficiaries experiencing significant delays accessing new treatments.

The undersigned support the creation of a legislative safe harbor for PIE and strongly encourage the House of Representatives to pass the *Pre-approval Information Exchange Act of 2022* (H.R. 7008). This bill will improve patient access to care by ensuring that the proactive provision of truthful and non-misleading economic and clinical information to payers prior to FDA approval does not run afoul of FDA labeling guidelines and prohibitions against off-label commercial marketing.

Sincerely,

Academy of Managed Care Pharmacy
Alliance of Community Health Plans
American College of Apothecaries
American College of Clinical Pharmacy
American Society of Health-System Pharmacists
Astellas Pharma US, Inc.
Aventine Consulting
Blue Cross Blue Shield Association
Council for Affordable Health Coverage
Humana
Little Hercules Foundation
Magellan Rx Management
Parent Project Muscular Dystrophy
Prime Therapeutics

PHOENIX
ZONES
INITIATIVE

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Testimony of
Hope R. Ferdowsian, MD, MPH, FACP, FACPM, Phoenix Zones Initiative
Before the Subcommittee on Health, Committee on Energy and Commerce
Thursday, March 17, 2022
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

Dear Chairwoman Eshoo, Ranking Member Guthrie, and members of the Subcommittee,

Thank you for the opportunity to provide written testimony in support of the FDA Modernization Act of 2021 (H.R. 2565 and S. 2952). This legislation is essential to encourage scientific and ethical innovation and to improve the lives of patients who are desperate for safer and more effective therapeutic interventions.

As a double board-certified internal medicine, preventive medicine, and public health physician, I have 20 years of experience treating patients who suffer from various medical and mental disorders that range from the top killers of Americans, including heart disease and cancer, to debilitating psychiatric disorders such as posttraumatic stress disorder and major depression. I regularly teach medical students, residents, and other healthcare professionals how to evaluate and treat patients living with these conditions.

Additionally, I have designed and led human clinical research trials and consulted with pharmaceutical companies on human and animal research ethics, and I have received National Science Foundation awards to investigate opportunities to advance scientific and ethical innovation in medicine. My publications on these subjects have appeared in peer-reviewed journals and popular science magazines. I have worked with professionals at government agencies, including the FDA and the NIH; executives at pharmaceutical companies; decision makers at health charities; and innovators at academic institutions around the world.

After serving on the faculty of the George Washington University School of Medicine and Health Sciences and the Georgetown University School of Medicine, I now serve as an associate professor of medicine at the University of New Mexico School of Medicine. Additionally, my professional responsibilities include acting as a medical expert for Physicians for Human Rights and as president and CEO of Phoenix Zones Initiative (PZI), an organization that advances the interconnected health and well-being of people, animals, and the planet through education, research, and advocacy. One of PZI's goals is to transform medical research in ways that benefit people and animals. My testimony is submitted in my role as a physician, scientist, educator, patient, and caregiver, and as president and CEO of PZI.

The Need for Greater Innovation

The FDA Modernization Act of 2021 is promising news for medicine and public health. This landmark legislation marks a major milestone in transforming medical research to embrace testing platforms that are more innovative and relevant to human health than are outdated, formulaic animal tests.

The science of nonclinical testing has been transformed over the past several decades, but in the absence of regulatory acceptance of more modern testing methods, practical change has occurred at a glacial pace that endangers the nation's health. Passage of the FDA Modernization Act will ultimately streamline drug development and stimulate innovation, benefitting both patients and those of us who care for them.

Views about animal experimentation are often presented in polarizing ways. Both defenders and skeptics of the scientific merits of animal experiments have made far-reaching claims that are frequently based on anecdotal evidence.

In human medicine, we rely on an evidence-based process to make clinical and population-based decisions. Similarly, in considering questions about the validity and reliability of animal testing and research, it is important to examine internal and external variables that affect study design as well as systematic analyses of the animal research literature.

When physicians and scientists have examined how animal experimentation translates to human outcomes, they have found serious problems with methodology, clinical relevance, predictive value, and the reproducibility of results.

Concerns about the predictive value of animal testing have led to dramatic changes in the field of toxicology, including a move toward an evidence-based, integrated, non-linear approach, which includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling. At each step, population-based data and human exposure information are considered, as is the question of what data are needed for decision-making.

Similar strategies are available and necessary for predicting the safety and effectiveness of various therapeutic interventions, including medications.

Drug absorption is a complex process that is dependent upon numerous biochemical and physiological factors. Animal tests have not been reliable predictors of bioavailability behavior in humans. Absorption, Distribution, Metabolism, Excretion, and Toxicology (ADMET) studies in animals repeatedly show that there is no clear relationship between human bioavailability and animal bioavailability, particularly in dogs, nonhuman primates, and rodents—animals who are commonly used in drug development. As a result, high rates of false negatives and false positives are common, which increases the risk for both adverse events in humans and delays in drug discovery. When researchers have analyzed the sum of published animal studies through systematic reviews and meta-analyses, they have likewise shown that the predictive value of animal studies in determining clear evidence of human benefit approximates the flip of a coin.

Discordance between animal and human studies can be explained by threats to internal and external validity in animal experimentation, including methodological flaws, publication bias, disease-specific disparities, profound differences in outcome measures, human genetic variability, and the effects of behaviors and the environment on gene expression.

Additionally, various unknown variables affect the validity and reproducibility of animal tests. The effects of captivity, maternal-infant separation, social isolation, and the induction of fear,

anxiety, pain, and discomfort in animals result in changes to their physical, mental, and physiological health and well-being. Decades of research in humans and animals have shown how adverse experiences affect the manifestation of multiple diseases. Various physical, cognitive, and emotional stressors influence immunological, endocrine, neurological, cardiovascular, and other organ systems. These problems are not resolved with improvements in traditional animal welfare standards or other standardization procedures.

As a result of these problems, executives and scientists at pharmaceutical companies and government agencies have expressed how a mandated overreliance on animal research impedes their work. Decision makers at these companies have privately shared that they fear the legal consequences of foregoing animal tests in the setting of existing regulatory requirements administered through the FDA.

The Need for Improved Oversight

The past six decades have marked a significant revolution in research ethics in the United States. Following several research scandals, in 1979, the Congressionally appointed National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published *The Belmont Report*, which established foundational ethical principles to guide research involving human subjects. *The Belmont Report* and resulting legal codifications dramatically transformed human research for the better. Human research now requires informed consent, a full assessment of the risks and benefits of research, and special protections for vulnerable individuals and populations such as children, who cannot provide informed consent.

The situation is much different for animals, who overwhelmingly bear the burdens of research, despite their inability to provide informed consent or to benefit from the research. The U.S. Animal Welfare Act still does not cover most animals used in research, and animals who are covered under the Animal Welfare Act are not protected from serious harm.

As a result, Americans have become increasingly skeptical of animal research. Roughly half of Americans think that medical testing on animals is morally unacceptable, and public opposition to animal research has steadily increased over the past decade because of moral, ethical, and scientific concerns.

Although the U.S. spends more on healthcare and research than does any other industrialized nation, high levels of spending do not translate into meaningful health outcomes or increased life expectancy. In fact, over the past twenty years, the percentage of deaths linked to preventable causes has remained about the same.

Scientific and ethical innovators should not be held back by an eighty-year-old misleading mandate that requires animal testing and slows progress. If government scientists and regulators require education and training on the latest innovative methods, it should be provided.

The FDA Modernization Act of 2021 will enable drug companies to test a drug's safety and efficacy using more advanced and ethical methods in place of animal testing wherever possible.

During the COVID pandemic, many of us realized that the drug and vaccine approval process needs to be overhauled. Fortunately, government and scientists brought urgency to the pandemic response, cut through organizational red tape, and developed successful vaccines in less than a year. Now is the time to bring this commitment and innovation to other areas of medicine for patients who need our help.

The FDA Modernization Act will free the FDA to allow for the best science to address the diseases that afflict patients.

Thank you for your attention to this important matter.

Sincerely,

Hope Ferdowsian, MD, MPH, FACP, FACPM
President and CEO, Phoenix Zones Initiative

NANCY MACE
1ST DISTRICT, SOUTH CAROLINA

COMMITTEE ON TRANSPORTATION AND INFRASTRUCTURE

COMMITTEE ON OVERSIGHT AND REFORM

COMMITTEE ON VETERANS' AFFAIRS

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March 16, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

RE: H.R. 2565, The FDA Modernization Act of 2021

Dear Chairwoman Eshoo and Ranking Member Guthrie,

As a proud cosponsor and co-author of H.R. 2565, the FDA Modernization Act, I write to express unequivocal support for legislation that would improve public-health policy while avoiding animal testing when a scientifically suitable alternative is available and approved by the Food and Drug Administration (FDA).

The intent of the FDA Modernization Act is to eliminate the animal testing mandate for new drug development that is found in statute and then to spur innovation that will quicken the pace of delivery and pricing of new drugs in the marketplace. The bill recognizes that scientific methods are continually advancing and our national science policy should allow for their use when they are superior. The changes to the Federal Food, Drug and Cosmetics Act called for in the FDA Modernization Act will not limit FDA authority. On the contrary, FDA will now have the authority to work with drug developers to use the best science in the vital realm of drug development.

American consumers face several dilemmas when it comes to the drugs they need: extraordinarily high costs for drugs, inordinately long wait periods in bringing the drugs to market, and, even after the drugs are approved for common use, serious health side effects for consumers often result from taking the drugs. The FDA Modernization Act will improve outcomes by allowing better cheaper methods of testing to be used.

PRINTED ON RECYCLED PAPER

The reality is pharmaceutical industry is burdened by outdated FDA statutes and regulations and this bill is a step toward remedying that problem.

Some testing strategies are not put into practical use because of FDA requirements to use animal testing strategies even when it's clear they produce inferior results, apart from their higher cost and longer time frame for completion. Animal tests, in large part, are not predictive of the human response to drugs, with 90 to 95 percent of drugs and vaccines found safe in animal tests failing during human clinical trials.

Where a scientifically recognized modern test method exists or a particular purpose, sponsors would have the option to use the test method in consultation with FDA.

While the FDA has claimed that statutory change is unnecessary and it has "discretion" to accept non-animal models in new drug submissions, a recent federal case (*Vanda Pharmaceuticals v. FDA*) addressed this issue in the context of clinical (human) trials. The Court's decision is unambiguous in directing drug developers who seek relief from the animal-testing mandate to turn to Congress and secure a statutory change. That's the prescription provided by the FDA Modernization Act.

The FFDCA has promoted the *status quo*, requiring traditional testing during preclinical studies, and creating an unreceptive environment that fails to encourage or support the development of modern and emerging test methods. Despite that intransigence, we are on the verge of the next phase of modern drug development with human-based models that can predict human drug response. Testing drugs on animals doesn't reflect 21st Century scientific advancement. H.R. 2565 and S. 2952 will be catalysts for this transition to modern science.

Congress and the FDA must unleash the power of science in overseeing U.S. drug development.

Sincerely,

Nancy Mace
Member of Congress

Subject: Testimony - March 17th Health Subcommittee HEARING ON "THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Testimony of International Autoimmune Encephalitis Society

Before the Subcommittee on Health, Committee on Energy and Commerce

Thursday, March 17, 2022

The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

International Autoimmune Encephalitis Society supports the FDA Modernization Act because it would:

- Authorize the use of the best nonclinical test method, animal-based or human-based, to determine the safety and efficacy of a new drug, whether animal or nonanimal.
- Broaden options for drug sponsors to usetest methods most likely to predict how a drug will react in humans, including state of the art nonclinical models based on human biology.
- Encourage innovation and use of 21stCentury science to improve success in clinical trials, bring more treatments to patients sooner and at less cost.

Best,

Tabitha Orth,

President,

International Autoimmune Encephalitis Society

www.autoimmune-encephalitis.org

IAES
International Autoimmune Encephalitis Society

AxoSim
Human Data, Faster.

March 17, 2022

To:

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Subject: Testimony - March 17th Health Subcommittee HEARING ON "THE FUTURE OF MEDICINE: LEGISLATION TO ENCOURAGE INNOVATION AND IMPROVE OVERSIGHT

AxoSim.com | 1441 Canal St., Ste 206 New Orleans, LA | 504.609.3469 info@axosim.com

AxoSim
Human Data, Faster.

March 17, 2022

Testimony of
Lowry Curley, PhD, PhD, CEO AxoSim Inc
Before the Subcommittee on Health of the Committee on Energy and Commerce
Thursday, March 17, 2022
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

On behalf of AxoSim Inc, a New Orleans biotech company that empowers advancements in human neuroscience and partners with biopharma to facilitate breakthroughs in the most devastating neurodegenerative diseases, I offer this testimony in support of the FDA Modernization Act of 2021 (H.R. 2565 and S. 2952).

This legislation broadens the scope of acceptable nonclinical models for drug development, enabling researchers to test a drug's safety and efficacy using more advanced and humane methods in place of animal testing where possible. Such an amendment, if enacted, could pave the way for faster, more effective, and more humane therapeutic development.

When the FFDCA was enacted in 1938, animal models seemed like the best way for drug developers to study how therapeutics might act within a biological setting. In theory, then, animal testing should ensure that only the safest, most effective drugs make it to clinical trials. Over the years, innovation has changed the equation, and better models are now available in many cases. Innovation in the years ahead will almost certainly produce superior methods than animal testing in nearly all cases.

Under the current regulatory scheme:

- 90 to 95 percent of drugs found safe in traditional nonclinical tests fail during human clinical trials due to toxicities not predicted by traditional animal tests or because of lack of efficacy, in large part, because animal data are not predictive of the human response.
- It takes from 10 to 15 years to develop a new drug, costing between $1 to $6 billion.
- Estimates suggest that, relative to *in vitro* models, animal testing is 1.5- to 30-times more expensive.

We can apply human biology-based test methods to better predict how humans will respond to drugs in clinical trials. We are already on the verge of the next phase of modern drug development and allowing for the use of only animal models doesn't reflect 21st Century scientific advancement. H.R. 2565 and S. 2952 will be catalysts for this transition to modern science.

Sincerely,

J. Lowry Curley

J. Lowry Curley, PhD
Co-Founder and CEO

Neuroscience Working Table

Working Together to Achieve a Neuroscience Center of Excellence

March 17, 2022

The Honorable Anne Eshoo
Chair
Subcommittee on Health
House Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
House Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

Statement for the Record on "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight."

Dear Chair Eshoo and Ranking Member Guthrie,

The Neuroscience Working Table ("Working Table"), which includes more than 40 organizations and coalitions representing more than 100 million Americans with psychiatric and neurologic diseases, writes to commend you for holding this important legislative hearing. One of the bills under consideration, H.R. 6000, would require the establishment of additional centers of excellence at the Food and Drug Administration (FDA) and enable the creation of a Neuroscience Center of Excellence (NCOE).

The Working Table supports the creation of a NCOE at FDA with the mission of accelerating the development, review, and approval of new medical products and achieving patient-centered regulatory decision-making through collaboration, engagement, and transparency. Establishing the Neuroscience Center of Excellence at FDA has been a bipartisan, bicameral priority. We appreciate the leadership of Reps. DeGette and Upton on the aforementioned H.R. 6000, *the Cures 2.0 Act*; Reps. Blumenauer, Pascrell, and Bacon on H.R. 5435, *the BRAIN Act*; and Senators Collins and Luján on S. 3427, *the Neuroscience Center of Excellence Act*.

Despite the large societal need, medical products for neurological and psychiatric diseases and disorders are approved by the FDA at a much lower rate than products for other disease areas. In recent years, FDA reviewers denied more requests for (and granted fewer) breakthrough therapy designations among neuroscience New Drug Applications (NDAs) than they did for NDAs in other disease areas. Consistent with the passionate pleas you heard at your July hearing entitled "The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases", we cannot wait another five years.

Given the success of the Oncology Center of Excellence,[1] the Working Table believes Congress should build on the model created by 21st Century Cures and enact legislation to establish a NCOE at FDA to tackle the significant unmet need faced by those living with psychiatric and neurologic diseases. Establishing the NCOE would accelerate development by:

- Placing a stronger emphasis on drug and device development tools for treatments and cures for psychiatric and neurologic diseases;
- Increasing utilization of patient-focused drug and device development for people living with psychiatric and neurologic diseases; and,
- Improving engagement between FDA and stakeholders (including patients) and strengthening internal coordination within FDA.

The NCOE should leverage regulatory scientists and reviewers with expertise in drugs, biologics, devices, and diagnostics to expedite development of drugs and devices for psychiatric and neurologic diseases. Leveraging this expertise and enabling further collaboration, within the agency and with outside experts, will be essential as psychiatric and neurological diseases present challenging scientific questions due to the complex pathologies of the diseases and heterogeneity of symptoms, among other reasons. Further, this NCOE should help promote equity and inclusion of traditionally underrepresented populations in the research and development of medical products. Finally, Congress should not only establish the NCOE but also ensure it has the necessary funding, consistent with the Oncology Center.

We agree with Former FDA Commissioner Scott Gottlieb who identified neuroscience as the next logical consideration for a Center of Excellence. When commenting about the possibility of future centers of excellence during testimony before Congress, Gottlieb said the OCE "is an organizational model that we seek to adopt in other settings" and "some of the areas under consideration are immunology and neuroscience."[2]

The establishment of the NCOE will help FDA prepare for the likely explosion in medical product applications involving psychiatric and neurologic diseases, coming as a result of significant private and federal government investments in the area. In H.R. 2471, *the Consolidated Appropriation Act, 2022*, Congress enacted the following: $2.2 billion for mental health research, an increase of $113 million over Fiscal Year 2021; $620 million for the BRAIN Initiative, an increase of $60 million; $25 million for the ACT for ALS; and $3.48 billion for Alzheimer's and related dementia research, an increase of $289 million. The private sector, despite the challenges in development, has made an even larger investment for research and development. To prepare the FDA for the likely explosion in neuroscience medical product applications, Congress should establish and fund the NCOE, similar to what it did in the oncology space. FDA should not be put in a position of being under-prepared and trying to play catch-up. Putting FDA in that position would not only hurt the Agency

[1] Additional background on the success of the OCE and its connection to a potential NCOE can be found here: https://leavittpartners.com/wp-content/uploads/2021/11/Understanding-the-FDAs-Oncology-Center-of-Excellence-Neuroscience-Working-Table-October-2021.pdf

[2] Testimony of Scott Gottlieb, M.D., FDA Commissioner before the Health, Education, Labor & Pensions Committee. 2017 https://www.help.senate.gov/imo/media/doc/Gottlieb5.pdf

but also those living with psychiatric and neurologic diseases and disorders, due to the likely delays.

We appreciate your consideration of our input as you continue to develop the user fee legislation and look forward to working with you, other Energy and Commerce Committee members, and our Congressional champions on this important issue. Should you have questions, please contact Clay Alspach at clay.alspach@leavittpartners.com, Josh Trent at josh.trent@leavittpartners.com, or Mark Roberts at mark.roberts@leavittpartners.com.

Sincerely,

The Neuroscience Working Table

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington, D.C. 20515

Testimony of
Allergy & Asthma Network
Before the Subcommittee on Health, Committee on Energy and Commerce
Thursday, March 17, 2022
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

Allergy & Asthma Network supports the FDA Modernization Act because it would:

- Authorize the use of the best nonclinical test method, animal-based or human-based, to determine the safety and efficacy of a new drug, whether animal or nonanimal.
- Broaden options for drug sponsors to use test methods most likely to predict how a drug will react in humans, including state of the art nonclinical models based on human biology.
- Encourage innovation and use of 21st Century science to improve success in clinical trials, bring more treatments to patients sooner and at less cost.

All my best,

Tonya A. Winders
President and CEO
Allergy & Asthma Network

President, 2017-2024

Global Allergy & Airways Patient Platform
8229 Boone Blvd., Suite 260
Vienna, VA 22182

AAFP
AMERICAN ACADEMY OF FAMILY PHYSICIANS

March 17, 2022

The Honorable Anna Eshoo
Chairwoman
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Brett Guthrie
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairwoman Eshoo and Ranking Member Guthrie,

On behalf of the American Academy of Family Physicians (AAFP) and the 127,600 family physicians and medical students across the country we represent, I applaud the committee for its continued focus to improve our health care system, including improving diversity and equity in research. I write in response to the "The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight" hearing to share the family physician perspective.

The AAFP has long advocated for better integration of primary care in our health care system. Primary care is the only health care component where increased access is associated with better population health and more equitable outcomes.[i] Often times, family physicians are the sole physicians providing care in their communities, especially in rural or underserved areas, and can adapt their care to fit the unique needs of these communities, utilize data to monitor and manage their patients, and use evidence-based science to prioritize services most likely to benefit health. Being on the front lines of health care, family physicians are uniquely positioned to serve as the foundation of a modernized, high-functioning health care system that can improve patient outcomes, address health inequities, and reduce costs.

The AAFP is working to develop strategies that improve population health and advance health equity through identifying and incorporating social determinants of health in all health care delivery systems – with the goal of prioritizing preventive health and management of chronic conditions. We support Health in All Policies as a strategy to improve population health and advance health equity, and developed a toolkit for physicians through the EveryONE Project. We are pleased to see that the Committee is considering legislation that is consistent with our "health in all policies" strategy.

The AAFP supports, **H.R. 3085, the Equity in Neuroscience and Alzheimer's Clinical Trials (ENACT) Act**, which would increase participation of underrepresented populations in dementia clinical trials by expanding education and outreach to these populations, encouraging the diversity of clinical trial staff, and reducing participation burden. This is critical to addressing the various health inequities associated with gender, race, and ethnicity in dementia care.[ii] Today, more than 6 million Americans are living with Alzheimer's, and family physicians, as a patients' first point contact with the health system, are ideally positioned to provide and coordinate care for individuals living with dementia from early to end stages of the illness.[iii]

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The Academy also supports, **H.R. 6584, the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act**, which would enhance reporting on clinical trial diversity and representation and provide resources, such as workshops and community health center grants, to underrepresented communities to improve access and participation in clinical trials. The AAFP supports the inclusion of diverse populations in clinical trials, surveys, and other research as an essential tool to better understand the drivers of health disparities and their impact on health, whether it be increased risk for disease or differences in treatment efficacy.

Lastly, the AAFP supports several provisions included in, **H.R. 6000, Cures Act 2.0**. Specifically, we are supportive of the provisions that increase diversity in clinical trials to reflect the diversity of today's patient population; leverage real-world data to create closer alignment between medical progress and patient need; improve health literacy to improve patient outcomes; extend Medicare telehealth flexibilities and strengthen telehealth access in Medicaid & CHIP; strengthen vaccines awareness and electronic exchange of immunization data; and advance solutions for individuals with long COVID. Similar to the original 21st Century Cures Act, Cures Act 2.0 reflects a goal to safely and efficiently modernize health care delivery, which is particularly necessary as we are still fighting the coronavirus pandemic.

Again, we thank the Committee for its work to improve our public health and health care system and ensure it can adapt to meet the needs of our growing, diverse patient population. We look forward to working with you to pass these important bills. If you have additional questions, please reach out to John Aguilar, Manager of Legislative Affairs at jaguilar@aafp.org.

Sincerely,

Ada D. Stewart, MD

Ada D. Stewart, MD, FAAFP
Board Chair, American Academy of Family Physicians

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[i] McCauley L, Phillips RL, Meisnere M, Robinson SK. (2021). "Implementing High-Quality Primary Care: Rebuilding the Foundation of Health Care." *National Academies of Sciences, Engineering, and Medicine*. Web.
[ii] Alzheimer's Association. (2022, January). *Special Report - More than Normal Aging: Understanding Mild Cognitive Impairment*. Alzheimer's Association. Retrieved March 15, 2022, from https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf
[iii] Ibid.

Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight"
March 17, 2022

Lucy Vereshchagina, Ph.D., Vice President, Science and Regulatory Advocacy, Pharmaceutical Research and Manufacturers of America

The Honorable Earl L. "Buddy" Carter (R-GA)

1. Dr. Vereshchagina, would you explain how H.R. 7032, the "Increasing Transparency in Generic Drug Applications Act," could limit patient access to new therapies by forcing companies to divulge highly valuable trade secrets?

Representative Carter, thank you for your question for the record regarding H.R. 7032, the "Increasing Transparency in Generic Drug Applications Act." I appreciated the invitation to testify before the United States House of Representatives Committee on Energy and Commerce, Subcommittee on Health, and welcome the opportunity to provide additional thoughts on this bill.

H.R. 7032 (the bill) would authorize FDA to disclose to generic drug applicants highly valuable proprietary information (including trade secrets and confidential commercial information) about the inactive ingredients in the reference listed drug (RLD). Specifically, the bill would authorize FDA to disclose information on the precise type and amount of inactive ingredients in a drug. Information about a drug product's formulation, including the precise quantities of inactive ingredients in a pharmaceutical product, typically constitutes a trade secret if it is not disclosed to the public.[1]

[1] *See, e.g., Enteris Biopharma, Inc. v. Clinical Pharmacology of Miami, Inc.*, 2015 WL 12085848, at *8 (S.D. Fla. Mar. 20, 2015) (denying a motion to dismiss a trade secret claim where the alleged trade secret included, among other things, a "proprietary excipient formulation for enteric coating of HPMC capsules . . ."); *Appleton v. FDA*, 451 F. Supp. 2d 129, 141 (D.D.C. 2006) (upholding, in a suit brought under the Freedom of Information Act (FOIA), FDA's withholding of information about "drug chemical composition" as trade secrets); *In re Gabapentin Patent Litig.*, 312 F. Supp. 2d 653, 660 (D.N.J. 2004) (affirming a magistrate judge's decision to require redaction of summary judgment papers because they contained an ANDA sponsor's trade secrets, based on a declaration stating that "[t]he composition statements . . . provide a recipe for making the products. Purepac would suffer serious commercial injury if the information became known to others."); *Citizens Comm'n on Human Rights v. FDA*, 1993 WL 1610471 (C.D. Cal. May 10, 1993), at *7 (upholding, in a FOIA suit, FDA's withholding of information because "an NDA by definition contains trade secret information because it contains significant information about how a pioneer drug product is formulated [and] chemically composed . . ."); *Myers v. Williams*, 819 F. Supp. 919, 921 (D. Or. 1993) (granting a preliminary injunction against the plaintiff's disclosure of the Halcion formula because "Upjohn has made a strong showing that the Composition Statement falls within the definition of a trade secret[.]").

The Bill Undermines the Long-standing Hatch-Waxman Amendments and Incentives for Innovative Drug Development

The broad disclosure of proprietary information that the bill would authorize would fundamentally alter the careful balance that Congress created in the Hatch-Waxman Amendments between encouraging innovation and facilitating access to generic drugs. Hatch-Waxman contemplates that a generic sponsor may avoid resource-intensive clinical trials by relying on FDA's approval of the innovator's drug without having access to the underlying data—not that FDA would disclose the innovator's proprietary information, such as confidential inactive ingredient information, to the generic sponsor as well.

By removing protections for innovators' proprietary formulation information, the bill would undermine incentives for development of novel pharmaceutical formulations that benefit patients. Drug product development is a time- and resource-intensive part of research and development. Disclosure of formulation information to generic sponsors would harm innovators by allowing competitors to potentially take advantage of innovators' formulations. Potential competitor uses include uses other than developing the generic drug at issue, such as to design around intellectual property or develop their own future formulations. The disclosure that the bill would authorize therefore would undermine innovator's investments in formulation research and development and erode protections on proprietary information.

The Bill is Unnecessary

In addition to limiting patient access to new therapies by forcing companies to divulge highly valuable trade secrets, the legislation is unnecessary. Indeed, the bill would allow disclosure of quantitative and qualitative inactive ingredient information even when FDA has not required or recommended that the inactive ingredients in a generic drug product be quantitatively and qualitatively the same in those as the RLD. H.R. 7032 would authorize FDA to share with generic drug applicants proprietary information about the inactive ingredients in the RLD, with the apparent goal of enabling generic applicants to more easily obtain approval. But the Federal Food, Drug and Cosmetic Act (FDCA) does not contemplate that this information will be shared with the generic sponsor or be needed for generic approval.

There is no general requirement under the FDCA that a generic drug product have the same inactive ingredients in the same concentrations as in the RLD.[2] Instead, the concept of qualitative and quantitative sameness of inactive ingredients ("Q1/Q2") at issue in the bill arises in two non-statutory contexts. First, under FDA's non-binding guidance for some products, inactive ingredient sameness may help an ANDA applicant to show its generic drug is bioequivalent to the RLD through a less costly or less time-consuming method. Second, FDA regulations (not the statute) impose Q1/Q2 sameness requirements for establishing bioequivalence and for approval of certain generic dosage forms, subject to exceptions.

More specifically, generic applicants must show the proposed generic drug is bioequivalent to the RLD to support approval.[3] Bioequivalence means that the drugs' rate and extent of

[2] *See* FDCA § 505(j)(2)(A).
[3] *Id.* § 505(j)(2)(A)(iv).

absorption in the body do not differ significantly.[4] For many drugs, bioequivalence can be shown by testing the drug's blood levels in simple clinical studies (in vivo studies) in healthy volunteers. For locally acting drugs, however, blood tests might be insufficient to show bioequivalence. The FDCA authorizes FDA to "establish alternative, scientifically valid methods" to show bioequivalence.[5]

In non-binding guidance for certain products, FDA offers ANDA applicants the choice of performing either in vivo or in vitro testing to satisfy the requirement to show bioequivalence, but may condition use of the in vitro option on a showing that the proposed generic product has the same inactive ingredients as those in the RLD in concentrations that are within five percent of the concentrations in the RLD. FDA describes this type of qualitative and quantitative sameness of inactive ingredients as "Q1/Q2."

Additionally, FDA's regulations require Q1/Q2 sameness in two circumstances. First, FDA considers bioequivalence to be self-evident without the need for additional data if a generic injectable, ophthalmic, or otic solution is Q1/Q2 to the RLD.[6] This approach has been described as a "solution biowaiver." Second, FDA requires that generic injectable, ophthalmic, otic, or topical products be Q1/Q2 to the RLD to use the ANDA pathway, subject to exceptions.[7]

Accordingly, any Q1/Q2 requirement or recommendation is a creation of FDA and not of Congress. FDA has ample authority to approve ANDAs without any Q1/Q2 requirement, and to recommend and accept bioequivalence methods that are not based on a showing of Q1/Q2 sameness. Therefore, the disclosure of proprietary information that the bill would authorize is not necessary to enable ANDA applicants to comply with any statutory requirement.

Moreover, the bill would not restrict the disclosure of proprietary inactive ingredient information to the limited circumstances where FDA has required or recommended Q1/Q2 sameness. Rather, the bill would broadly authorize disclosure of such proprietary information about the RLD, even where such information is unnecessary to satisfy any FDA requirement or recommendation—or to the apparent intent of facilitating generic approvals.[8]

The Bill Raises Constitutional Issues

Disclosure of proprietary information as required by the bill also would raise constitutional issues under the Takings Clause of the Fifth Amendment to the U.S. Constitution.[9] This constitutional concern arises because the bill would interfere with sponsors' property rights, including their reasonable investment-backed expectation—rooted in the statutes and regulations

[4] *See id.* § 505(j)(8)(B).
[5] *Id.* § 505(j)(8)(C).
[6] 21 C.F.R. § 320.22(b)(1).
[7] 21 C.F.R. § 314.94(a)(9)(iii)-(v).
[8] In this way, the bill would go well beyond FDA's current practice of reviewing a proposed generic formulation for Q1/Q2 sameness to the RLD, which is limited to situations where FDA recommends or requires Q1/Q2 sameness in a regulation or guidance. FDA, Guidance for Industry, *Controlled Correspondence Related to Generic Drug Development*, at 12 (Dec. 2020) ("Consistent with the Agency's past and current practices, FDA does not intend to review proposed formulations that are neither required by regulation nor recommended in guidance to be Q1/Q2 to the RLD.").
[9] U.S. CONST. amend. V.

cited above governing disclosure[10]—that FDA will not disclose an RLD sponsor's proprietary inactive ingredient information. The bill therefore would effect a prohibited "taking" in the absence of just compensation, potentially subjecting the government to significant liability.[11]

[10] *See supra* note 4.

[11] *See Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1020 (1984); *see also Penn Cent. Transp. Co. v. City of New York*, 438 U.S. 104, 124 (1978) (establishing test for regulatory takings); *Lucas v. S.C. Coastal Council*, 505 U.S. 1003, 1019 (1992) (establishing test for takings based on deprivation of all economically viable use of affected property).

Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight "
March 17, 2022

Cartier Esham, Ph.D., Chief Scientific Officer, Executive Vice President, Emerging Companies, Biotechnology Innovation Organization

The Honorable Michael C. Burgess, M.D. (R-TX)

1. To build off 21st Century Cures Act, I introduced the FDA Advancing Collection of Transformative Science (FACTS Act). The FACTS Act will help cut red tape to create efficiencies and streamline the transition between an emergency use authorization (EUA), premarket submission, and permanent marketing authorization, all without cutting corners or jeopardizing safety requirements. Our nation has experienced a historical response in the development of therapeutics and vaccinations to combat this virus. In fact, Dr. Fauci advised that it would be at least one year until Americans would receive a COVID-19 vaccine. Well, here we are today with two vaccines and many effective therapeutics. It has truly been history in the making. However, it is also important that the FDA utilizes data generated from patients using effective therapeutics and vaccines that have been granted through EUA process. The FDA should be taking this data into consideration. It is no secret that one of the FDA's commitments is related to enhancing the way that we use real world data.

    a. How can real world evidence be used to complement clinical trials?

Randomized control trials (RCTs) are designed to provide evidence of drug efficacy and are the gold standard for comparing treatments. However, there are circumstances where a randomized control trial is not possible (e.g., rare diseases and other disease/therapeutic areas with small patient populations). In those circumstances, the use of real-world evidence can be used as an external control arm in the clinical trial to estimate the comparative treatment effect of the drug.

    b. Should there be any guardrails on the safety and utilization of real-world evidence?

The 2018 Framework for FDA's Real-World Evidence Program provides guardrails on the safety and utilization of real-world evidence. This framework specifies a three-part approach to evaluating the potential use of RWE to support changes to labeling about drug product effectiveness:

a. Whether the RWD are fit for use
b. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question, and
c. Whether the study conduct meeting FDA regulatory requirements (e.g., for study monitoring and data collection)

Hence, this approach highlights the regulatory considerations and guardrails in leveraging real-world data to support regulatory decision making.

c. Are there ways that we can improve and modernize the way we collect data from electronic health records and claims?

Yes, there are ways that we can improve and modernize the way we collect data from electronic health records and claims. Recently, FDA published draft guidance on Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products. In response to this draft guidance, BIO highlighted the need to identify best practices for data curation, processing and governance. Our recommendation included FDA working with stakeholders to better understand and address the practical realities of data curation, processing and governance as FDA is in the unique position to bring together all of the relevant stakeholders to understand the expectations for real world data (RWD) quality. It is imperative to work with health technology organizations that generate RWD and host workshops with all stakeholders to better understand these issues and help identify ways to meet Agency expectations.

d. Do you believe real world evidence promotes and advances personalized medicine for individuals and for the population at large? Can you explain how this works and how it will affect public health overall?

Yes, real world data and evidence have the potential to promote and advance personalized medicine for individuals and for the population at large. By definition, real world data are data relating to patient health status and/or the delivery of health care routinely collected from variety of sources and real world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data. Having a more robust understanding of how a drug or treatment works in the real world setting can help support approval of new indications for drugs or help support or satisfy post approval study requirements which can provide patients more timely access to innovative medicines.

e. Do you believe that implementing real world evidence techniques into the FDAs regulatory body will help advance innovation in oncology and the rare disease world?

Yes, the use of real world evidence to support FDA's regulatory decision making will help advance innovation in drug development, including in oncology and the rare disease space. For rare diseases and other disease/therapeutic areas that

have small or limited patient populations such as pediatrics, conducting a traditional clinical trial is not feasible and/or unethical. Hence, the use of real world data and evidence, offer patients hope for the promise of new and innovative medicines.

2. While the FFDCA makes clear that the FDA has the authority to approved drugs that not only treat disease but also prevent disease, the FDA historically has taken a very conservative approach to approving preventive products – even suggesting in the past that preventive products should face a higher evidentiary bar than traditional products that treat people after they become sick. Yet the ability to prevent disease, or the progression of disease, seems as important, if not more important, than treating disease after it has taken hold in a patient's body. Indeed, costs are higher, and outcomes are worse the longer it takes to catch and intervene against disease.

    a. Does the FDA still believe that preventive products should face a higher approval bar, and if so, why?

All products developed to prevent disease are reviewed by the FDA and held to the same evidentiary standards for safety and effectiveness as those products developed to treat disease. In the example of the use of aspirin for primary prevention of heart attack and stroke, FDA did find that the available evidence supported the use of aspirin for *secondary* prevention of heart attack and stroke, meaning that aspirin could prevent another heart attack or stroke in patients who have already had a heart attack or stroke. More recent examples such as for prevention of migraines, HIV infection and post-exposure prophylaxis for prevention of COVID-19 demonstrate the FDA's efforts to approve drugs to prevent disease.

3. Under the Accelerated Approval pathway, the FDA has the authority to rely on both surrogate and intermediate endpoints to predict likely clinical benefit for patients with serious unmet medical needs, rather than delaying approval until confirmatory trials can be completed that conclusively show clinical benefit.

    a. While surrogates like tumor shrinkage in cancer patients are a typical basis for Accelerated Approval, what other methods does the FDA permit sponsors to use in terms of predicting likely clinical benefit, particularly when involving preventive products whose clinical benefit is preventing the onset or progression of disease? And has the FDA considered the ability to rely on advanced technologies such as AI, machine learning, and advanced computational and analytical techniques to aid in the predictive analysis?

The FDA defines "clinical benefit" as a positive therapeutic effect that is clinically meaningful in the context of a given disease. For Accelerated Approval, phase 4 confirmatory trials are conducted by the sponsor to confirm the clinical benefit. Other

surrogate endpoints that have been the basis for accelerated approval include, but are not limited to:

- Prolonged suppression of HIV viral load in plasma has been shown to reduce the morbidity and mortality associated with HIV disease and has been the basis for Contains Nonbinding Recommendations 18 traditional approval. Shorter-term suppression of viral load has been used in the past as a surrogate to support accelerated approval because it was considered reasonably likely to predict an effect on morbidity or mortality. Data now demonstrate that short-term suppression of viral load may support full approval, in some circumstances.
- Clearance of bacteria from the blood stream as evidenced by a laboratory measurement of bacteria in the blood has been considered reasonably likely to predict the clinical resolution of infection.
- Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis.
- Decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body.
- Radiographic evidence of tumor shrinkage (response rate) in certain cancer types has been considered reasonably likely to predict an improvement in overall survival.

The PDUFA VII Commitment Letter includes provisions for a pilot Advancing the RWE program which specifically highlights the use of RWE in postapproval studies. Also, within the PDUFA VII Commitment Letter are provisions around enhancing the use of digital health technologies (DHT) in drug development and review. These provisions provide FDA with the resources to establish a DHT framework to guide the use of DHT-derived data in regulatory decision making for drugs and biological products. These provisions afford the FDA the opportunity to have workshops, conduct demonstrations products and issue guidance on use of DHTs. These PDUFA VII provisions will allow FDA to better consider ways to rely on advanced technologies such as AI, machine learning, and advanced computational and analytical techniques to aid in the predictive analysis.

The Honorable Earl L. "Buddy" Carter (R-GA)

1. Dr. Esham, would you explain how H.R. 7032, the "Increasing Transparency in Generic Drug Applications Act," could limit patient access to new therapies by forcing companies to divulge highly valuable trade secrets?

BIO supports innovation in drug development to improve patient access to new and innovative medicines. Forcing companies to divulge highly valuable trade secrets may create disincentives in the marketplace that could adversely limit patient access to new therapies. Hence, it is important to fully understand what the problem is that HR 7032 is trying to address and making sure that we take into account existing Hatch-Waxman and BPCIA provisions.

Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight "
March 17, 2022

Jeff Allen, Ph.D., President and CEO, Friends of Cancer Research

The Honorable Michael C. Burgess, M.D. (R-TX)

1. It seems to me as though the goal for ARPA-H is to bring into focus our domestic R&D efforts to address some of the larger challenges in health care. However, I stand by the viewpoint of being intentional and not duplicative with funding and believe that there needs to be additional conversations on structure of the agency. The original intent of Center for Medicare and Medicaid Innovation Center was to fuel innovation. Are there suggestions you have for reforms to other agencies or programs such as CMMI, that could save dollars and prevent duplication within ARPA-H?

While the overarching goal of facilitating innovation may be shared, the focus of CMMI and the mechanisms that CMMI and ARPA-H utilize will enable a quite different scope of work. CMMI has leveraged its ability to conduct pilot projects to explore innovation in payment models to help support optimization and efficiencies for Medicare beneficiaries. ARPA-H will provide direct funding and contracting intended to support work much earlier in the innovation cycle including transformational capabilities with broad application across multiple disease areas.

ARPA-H should embrace the goal of developing advanced proofs of concept for breakthrough technologies with the aim of transference of intellectual property rights—or licensing options—to a partner with capacities to move those technologies forward through development and commercialization. Internal pursuit within the agency of medical product development and commercialization should be the exception and should be considered only where the private sector declines licensing and development due to a perceived absence of commercial market or where there exists a compelling reason to retain ownership in the public domain. This is a focus that is unique from any other current government program at this scale.

   a. If ARPA-H was to be established, are there additional qualities or structural aspects from other agencies that can be applied to its design?

Given the origins of ARPA-H are deeply rooted in previous efforts in other sectors, it will be important for ARPA-H to adopt operational aspects that have been successful for DARPA and ARPA-E. These may include:

- **A Director, appointed by the President and reporting to the Secretary of HHS** along with any such other direct report that may be appropriate given the placement of the agency**,** with a time-limited appointment (e.g., 4 – 8 years). He/she will have full authority to establish ARPA-H as a DARPA-like contracting agency, with contracts developed by in-house program managers who select external performers, and maintain, enhance, or terminate projects based on performance against explicit milestones. ARPA-H will set priorities to define and advance the mission of the agency as informed by a multi-sectoral board of advisors.

- **World-class program managers** who define their programs, set milestones, track progress, and communicate with leaders in the healthcare, biomedical research, and technology sectors to identify new challenges and potential solutions. As in DARPA and ARPA-E, these program managers may be recruited from industry, academia, and government for a specific length of time (e.g., 3- 5 years) for what will be viewed as a coveted 'sabbatical', allowing them to work in a unique environment supportive of collaborative, time-bound, results-driven innovation.

- **Funding available for and the ability to contract with a broad range of institutions** including universities, national labs, public sector organizations, private companies, and nonprofits.

- **Funding directed through milestone-driven contracts** of a sufficient size (up to multiple millions annually) that are structured to support high-risk ventures, allow unsuccessful ventures to fail fast and allow successful projects to proceed with the expectation that this rapid, high-risk approach will yield high rewards.

- **Latitude to appoint advisors.** Similar to ARPA-E, the Director should be given latitude to draw from existing advisory committees appointed by the Secretary of HHS or to create a new advisory committee unique to the agency to advise on specific program tasks or overall direction of ARPA-H.

In addition, the autonomy of ARPA-H should be enabled with additional flexibilities such as the authority to submit its annual budget request directly to Congress concurrently with its submission to the Office of Management and Budget.

b. Are there any consequences to ARPA-H being housed in NIH?

Hopefully the main result of ARPA-H being housed in NIH will be expedited processes for establishing the agency by leveraging current infrastructure (e.g., hiring processes, employee benefits, transferring of funds, etc.). Recognizing that the potential strength of ARPA-H will be its unique programmatic focus and approach, additional authorizing language can help maintain its appropriate independence while allowing ARPA-H to capitalize on current NIH capabilities.

2. I've noticed that the ARPA-H text calls for the establishment of an "Interagency Advisory Committee." A few examples of the participants include the Director of NIH, Commissioner of FDA, the Director of the CDC, and the list goes on.

    a. Is there a plan or benefit to these individuals working with stakeholders who have actual expertise and experience?

There would certainly be a benefit for ARPA-H to have regular collaboration with and advisement from subject matter experts. The Interagency Advisory Committee's role is to ensure projects align with the needs of the healthcare continuum. The committee's interactions with members of ARPA-H will likely largely be with project managers. In turn, the project managers will ensure that the right expertise from both the public and private sectors can help inform each specific project. Future authorizing language may help establish processes to balance any potential conflicts of interest from external collaborators and facilitate robust interactions.

3. Millions of Americans suffer from some form of psychiatric and neurologic diseases. In my home state of Texas, thousands of people suffer from Alzheimer's disease, Parkinson's disease, and other diseases or disorders of the central nervous system. Despite this, FDA reviewers denied more requests for (and granted fewer) breakthrough therapy designations among neuroscience New Drug Applications (NDAs) than they did for NDAs in other disease areas. In 2017, the FDA established a Center of Excellence focused on oncology products. And since then, the agency has seen a demonstrable increase in the number of applications and approvals of oncology products. The FDA's Oncology Center of Excellence is viewed by FDA, patients, and other stakeholders as a strong success. I believe the Committee should build on these successes by establishing a Neuroscience Center of Excellence as part of our work on the FDA user fee legislation.

    a. Can you offer your view on how a Neuroscience Center of Excellence can help accelerate the review and approval of more medical products to confront neurological diseases and disorders like Alzheimer's disease, ALS, autism, Parkinson's disease, and MS benefit the millions of Americans suffering from these diseases?

The establishment and success of the Oncology Center of Excellence is largely driven by the wealth of underlying scientific knowledge supporting cancer research, development, and care. As cancer treatments have become more complex and involve multiple types of products, multiple medical centers at FDA become involved. For example, diagnostic tests used to identify patients likely to benefit from a targeted treatment are regulated in the Center for Devices and Radiological Health and cellular therapies are regulated in the Center for Biologic Evaluation and Research. Due to this multi-modal approach to treatment, it was clear that a centralized group of oncology experts was necessary to coordinate cancer-related activities across the different FDA medical product Centers and to ensure consistency, efficiency, and optimal expertise.

In considering establishing additional Centers of Excellence for other therapeutic areas, it may be helpful to evaluate areas of potential disconnect or duplication of activities at FDA that would

benefit from increased synergy related to a specific disease state (e.g., Neuroscience), as well as the strength of scientific evidence and therapy development in the given therapeutic area.

Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight "
March 17, 2022

Reshma Ramachandran, M.D., Chair, Doctors for America FDA Task Force, Physician-Fellow, Yale National Clinician Scholars Program, Yale School of Medicine

The Honorable Debbie Dingell (D-MI)

Thank you, Representative Dingell for these thoughtful questions. Please find my responses below. I would also be happy to meet with your office to discuss these questions and my responses further.

1. *Dr. Ramachandran, it was good to see the thoughtful feedback on Cures 2.0 that you put into your written testimony. As we consider Cures 2.0, what more can this Committee do to ensure we are preserving those high standards of evidence at FDA?*

   First, Title III of Cures 2.0 includes several provisions focused on the FDA with an emphasis on efforts to expedite regulatory review of novel health technologies where the Committee could further ensure preservation of rigorous evidentiary standards at FDA as follows:

   - **Section 302 ("Grants for Novel Trial Designs and Other Innovations in Drug Development")** – Under this section, the FDA would award grants for the incorporation of novel trial designs and other innovative mechanisms, prioritizing the use of digital health technologies and real-world evidence, as well as the collection of patience experience data into clinical protocols and applications for drugs. While pilot testing of such approaches is necessary to ascertain feasibility as well as the benefits and harms in doing so, FDA should enable public availability of the evidentiary data generated to allow for independent review outside of the agency. **At a minimum, FDA should release a briefing document with summary results and their interpretation of the data as they typically do for other drugs and devices to allow for further validation of these novel trial designs and innovative mechanisms by independent experts and to inform the feasibility of using these methods for regulatory decision-making. However, FDA could also convene a public stakeholder meeting to discuss the use of these novel mechanisms to elicit further feedback on the feasibility of such approaches and where there might be opportunities for enhancing such approaches to ensure robust evidentiary standards. Moreover, FDA in awarding such grants for use of incorporating complex, adaptive and other trial designs into clinical protocols could also enable public access to how**

these funds are used, offering insight on how such approaches affect clinical trial costs.

- **Section 303 ("FDA Cell and Gene Therapy) and Section 307 ("Accelerating Timeline for Breakthrough and RMAT Designations")** – Under these sections, FDA would be tasked for producing a report to Congress on the landscape of cell and gene therapies and how the agency intends to address any challenges in the regulatory review process of such therapies. Additionally, FDA would also be able to award the designations of "Breakthrough Therapies" or "Regenerative Medicine Advanced Therapies (RMAT)" earlier in the drug development process allowing sponsors to further expedite development as well as review of their candidate drugs and engage with the FDA more closely. **Within these sections, the Committee could request FDA also report on the evidentiary standards for approval as well as their oversight of postapproval studies for these novel therapies. Congress could also go further to ensure rigorous evidentiary standards for approval and also, require postapproval studies to confirm clinical benefit and safety.** Prior research has shown that FDA-approved drugs awarded breakthrough designations are approved more quickly based on weaker evidence including trials that lack randomization, double-blinding, or control groups, use surrogate endpoints, and enroll fewer patients.[1] Our examination of the five novel gene therapies approved by the FDA as of the end of 2020 and had received the RMAT designation were approved more quickly based on even weaker clinical trial evidence than breakthrough therapies – most were approved based on a single, one-arm, open-label trial using surrogate endpoints.[2] However, despite this lack of robust evidence, only for three of the five treatments did FDA require postapproval studies. Thus, the focus of the FDA cannot be solely on expediting approval of these treatments, especially at the expensive of scientific evidence to inform clinical decision making for both patients and clinicians.
- **Section 304 ("Increasing Use of Real World Evidence)** – Under this section, the FDA would be required to issue guidance on the use of real-world evidence (RWE) in evaluating the safety and efficacy of drugs that received breakthrough status, fast track, or accelerated approval designations. FDA would also be required to submit a report to Congress on approaches for using RWE with recommendations for other legislative proposals towards implementing such approaches. This section also establishes a Real World Evidence Task Force under the Department of Health and Human Services that would provide further recommendations. **While these recommendations may further enable FDA to increasingly consider RWE in their regulatory decision-making process, they must be balanced with ensuring that such utilization is robust, can feasibly provide insight on the safety and efficacy of treatment candidates as clinical trials do, and serves as a useful complement to traditional clinical trials.** Moreover, the Real World Evidence Task Force fails to include independent experts and other public stakeholders without ties to industry sponsors – these perspectives for such a task force are imperative for ensuring that FDA and other agencies in HHS carefully consider the use of RWE in regulatory decision-making.
- **Section 309 ("Post-Approval Study Requirements for Accelerated Approval)**

Under this section, required postapproval studies meant to confirm clinical benefit for accelerated approval drugs would be allowed to be based on RWE. However, prior research has shown such confirmatory studies for accelerated approval cannot be feasibly replicated using available RWE in the form of electronic health records and medical claims.[3] Other forms of RWE proposed in the section to be the basis of postapproval studies such as clinical care data repositories and patient registries are insufficient as they are often limited to a single episode of care, often limiting their ability to provide longitudinal data. Moreover, such registries often do not include a control group making it difficult to determine the safety and efficacy of products in comparison to placebo or comparator.[4] Finally, most registries are owned by medical professional societies, but are funded by the pharmaceutical industry and thus, fail to include data on comparative effectiveness to examine treatment effect in relation to the standard of care or other alternatives. **Thus, Congress should amend this section to remove this section or only allow the use of RWE as a complement to traditional clinical trials in confirming that an accelerated approval drug has proven clinical benefit.**

Transparency of FDA's Utilization of New Approaches to Evidence Generation in Regulatory Decision Making

As with its predecessor, the 21st Century Cures Act, Cures 2.0 has a focus around accelerating the development of medical products through use of complex, adaptive trials, decentralized trials, and real-world evidence. While these novel mechanisms hold promise in enhancing the efficiency of evidence generation to more quickly inform regulatory decision-making, Congress must also ensure that safeguards around the use of such approaches are also included in Cures 2.0 and other associated legislation. **These safeguards must be structured to ensure independent evaluation and determination that these methods can provide evidence of meaningful clinical benefit and safety of medical products.** These might include:

- Allowing public access to the data generated through these new approaches;
- Requiring FDA to publish their reviews evaluating data generated through these new approaches that informs regulatory decision-making (as the agency currently does for all new product approvals within their review documents that are publicly posted on the Drugs@FDA database; such reviews are only available for original indication approvals, but not supplemental indications approvals, thus obscuring FDA's rationale for such approval decisions);
- Mandating advance registration of non-traditional studies and results reporting onto ClinicalTrials.gov as required under the FDA Amendments Act of 2007 with similar enforcement penalties should sponsors not comply including warning letters, fines, and legal action;[5]
- Engaging independent experts and other public stakeholders, not solely government officials and industry representatives together to discuss how FDA should incorporate these new mechanisms in their regulatory decision-making; and

- Evaluation by independent experts (e.g. academic partners, National Academy of Medicine, etc.) to study the feasibility of such approaches in informing clinical decision-making.

Independent Assessment of FDA's Expedited Review Pathways

Increasingly, FDA has approved new drugs and devices through expedited review pathways that allow for shorter regulatory review times at the expense of ensuring rigorous evidentiary support. Prior research has shown that pivotal clinical trials supporting such approvals over time are often shorter, enroll fewer patients, and lack characteristics of rigor including randomization, double-blinding, or active comparators.[6] Several expedited review pathways now exist across therapeutic areas allowing for such a tradeoff between speed and certainty of a medical product's safety and efficacy. **Congress could call for an independent review of all of FDA's expedited review pathways to determine whether the pathways are meeting their intended goals of ensuring patients timely access to drugs with meaningful clinical benefit, addressing diseases of unmet need.**

Alignment between the Centers for Medicare and Medicaid Services (CMS) and FDA

Cures 2.0 as written seeks to harmonize decisions made by the FDA on regulatory approval of new medical products with that of the Centers for Medicare and Medicaid Services (CMS) – in the wrong direction. As mentioned previously, drugs and devices have been increasingly approved by the FDA more quickly, but based on lower standards of evidence, heightening uncertainty at the time of approval of their efficacy and safety for patients and clinicians.[6,7] For certain types of drugs, such as those approved under the accelerated approval pathway, FDA requires manufacturers to complete confirmatory postapproval studies demonstrating clinical benefit. For other drugs, FDA can issue postmarketing requirements upon approval that would mandate manufacturers complete additional studies by a certain date. For those medical products where there remains uncertainty of safety and efficacy, CMS has the authority to review preapproval clinical trial evidence in making coverage decisions for their beneficiaries. In the case of aducanumab, CMS employed such an approach under the Coverage for Evidence Development (CED) program to require the manufacturer conduct a randomized-controlled trial evaluating the clinical efficacy and safety of the drug in representative populations.[8] This offers an opportunity for CMS and FDA to further collaborate in ensuring alignment of postapproval studies, particularly for those medical products approved through expedited review pathways where confirmation of safety and efficacy has yet to be proven and additional studies may be required by CMS in making coverage decisions. **Congress could mandate such coordination between FDA in establishing postmarketing requirements for approved medical products and CMS in making coverage decisions that may necessitate further evidence for certain drugs and devices including those receiving Breakthrough Therapy/Breakthrough Device designations or accelerated approval where uncertainty of their efficacy and safety remains at the time of FDA approval.**

Lessons Learned from COVID-19

Finally, many legislators have called for the passage of Cures 2.0 in the setting of the ongoing COVID-19 pandemic, noting the successful development of multiple vaccines, therapies, and diagnostics. FDA's efforts to instill public trust through increased utilization of their independent expert advisory committees for reviewing clinical trial evidence for COVID-19 vaccines and other therapies as well as transparency of their decision-making process in these authorization and approval decisions should be applied beyond the public health emergency period to treatments of other diseases.[9] One recent study found that for other disease areas, FDA has less often referred approved drugs while they were being considered for regulatory review to the agency's independent expert advisory committees over the past decade, from 55% to 6% annually.[10] Moreover, as called for by the current FDA Commissioner prior to his current tenure,[11] timely public access to clinical trial results, particularly during a public health emergency, is urgently needed to prevent duplication of efforts, stewardship of federal research funds, and inform clinical decision-making.

2. *Some stakeholders have raised concerns that if we insist on program integrity in the accelerated approval pathway, it will limit the chances for a rare disease drug getting approved. The accelerated approval pathway was originally created to get at diseases where other treatments are unavailable, so I want to make sure we are clear about this. Dr. Ramachandran, is there any provision of the Accelerated Approval Integrity Act which could limit opportunities to approve drugs that treat rare diseases?*

The Accelerated Approval Integrity Act does not include any provisions that would limit opportunities to approve drugs that treat rare diseases. The bill does not propose changes in the process for granting accelerated approval for potentially promising treatments. Under this legislation, the accelerated approval pathway remains intact. Instead, the bill as written would ensure that manufacturers fulfill their mandate of conducting postapproval studies to confirm the predicted clinical benefit that their initial accelerated approval was based on. By allowing FDA adequate oversight of these required confirmatory studies to ensure their timely completion, patients with rare diseases (and clinicians who treat them) will have greater and more timely certainty of the drug's potential clinical benefit. This will prevent patients from prolonged exposure to any undue harms – both clinically and financially – of continuing to take a drug, which may not demonstrate meaningful therapeutic benefit and delaying their opportunity to switch to other potentially more effective options (pharmacological or otherwise). As an example, the rare disease drug, duvelisib, received accelerated approval by the FDA for thyroid cancer and had a black box warning of having "fatal and serious toxicities" in 2018.[12] The manufacturer made no effort to conduct the required postapproval study necessary to confirm clinical benefit, allowing the drug to continue to be prescribed with these serious side effects to patients on the hope of a clinical benefit that outweighed these risks. Only last year, did the FDA request the manufacturer withdraw the drug from the market, which they eventually did earlier this year after recouping millions of dollars from sales annually. Thus, the Accelerated Approval Integrity Act as originally written with the automatic expiration for accelerated approval drugs where manufacturers fail to

conduct confirmatory studies or fail to demonstrate proven clinical benefit would protect patients. The bill also includes flexibility for the FDA to work with sponsors in implementing its key provisions, recognizing that for certain diseases and drugs, there may be additional considerations in establishing their study protocol for such confirmatory studies and their deadlines for completion.

References:

1. Puthumana J, Wallach JD, Ross JS. Clinical Trial Evidence Supporting FDA Approval of Drugs Granted Breakthrough Therapy Designation. *JAMA*. 2018;320(3):301-303. doi:10.1001/jama.2018.7619

2. Puthumana J, Egilman AC, Ramachandran R, Naushad N, Shah N, Ross J. Early experience with the FDA's regulatory review of novel gene therapies. *BMJ Evid Based Med*. Published online October 11, 2021:bmjebm-2021-111720. doi:10.1136/bmjebm-2021-111720

3. Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. *JAMA Network Open*. 2021;4(11):e2133667. doi:10.1001/jamanetworkopen.2021.33667

4. Dhruva SS, Ross JS, Desai NR. Real-World Evidence: Promise and Peril For Medical Product Evaluation. *P T*. 2018;43(8):464-472.

5. Food and Drug Administration. Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. Published online August 2020. Accessed August 18, 2021. https://www.fda.gov/media/113361/download

6. Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017. *JAMA Netw Open*. 2020;3(4):e203284. doi:10.1001/jamanetworkopen.2020.3284

7. Johnston JL, Dhruva SS, Ross JS, Rathi VK. Early experience with the FDA's Breakthrough Devices program. *Nat Biotechnol*. 2020;38(8):933-938. doi:10.1038/s41587-020-0636-7

8. Centers for Medicare & Medicaid Services. National Coverage Analysis: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Published online January 11, 2022. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305

9. Gupta R, Schwartz JL, Ross JS, Kanter G. During COVID-19, FDA's Vaccine Advisory Committee Has Worked To Boost Public Trust – It Can Still Do More. Health Affairs Blog. Published February 26, 2021. Accessed January 26, 2022. https://www.healthaffairs.org/do/10.1377/forefront.20210225.712221/full/

10. Daval CJR, Sarpatwari A, Kesselheim AS. Unwanted Advice? Frequency, Characteristics, And Outcomes Of Negative Advisory Committee Votes For FDA-Approved Drugs. *Health Affairs*. 2022;41(5):713-721. doi:10.1377/hlthaff.2021.01927

11. Califf RM, Zarin DA. Complete, Rapid Reporting of Clinical Trials: A Necessary Component of the Pandemic Response. Medium. Published January 4, 2021. Accessed May 5, 2022. https://califf001.medium.com/complete-rapid-reporting-of-clinical-trials-a-necessary-component-of-the-pandemic-response-aa158eb1a1cb

12. UPDATED: How a pharma company bought 2 accelerated approvals — never ran confirmatory trials — and cashed in until FDA said stop. Endpoints News. Accessed May 5, 2022. https://endpts.com/how-a-pharma-company-bought-2-accelerated-approvals-never-ran-confirmatory-trials-and-cashed-in-until-fda-said-stop/

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