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FDA USER FEE AGREEMENTS: ADVANCING MEDICAL PRODUCT REGULATION AND INNOVATION FOR THE BENEFIT OF PATIENTS, FDA CENTER DIRECTORS

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED SEVENTEENTH CONGRESS

SECOND SESSION

ON

EXAMINING FOOD AND DRUG ADMINISTRATION USER FEE AGREEMENTS, FOCUSING ON ADVANCING MEDICAL PRODUCT REGULATION AND INNOVATION FOR THE BENEFIT OF PATIENTS AND FOOD AND DRUG ADMINISTRATION CENTER DIRECTORS

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C O N T E N T S

STATEMENTS

TUESDAY, APRIL 26, 2022

FDA USER FEE AGREEMENTS: ADVANCING MEDICAL PRODUCT REGULATION AND INNOVATION FOR THE BENEFIT OF PATIENTS, FDA CENTER DIRECTORS

Tuesday, April 26, 2022

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

The Committee met, pursuant to notice, at 10:02 a.m., in room 430, Dirksen Senate Office Building, Hon. Patty Murray, Chair of the Committee, presiding.

Present: Senators Murray [presiding], Baldwin, Hassan, Rosen, Hickenlooper, Burr, Collins, Cassidy, Braun, and Marshall.

OPENING STATEMENT OF SENATOR MURRAY

The CHAIR. The Senate, Education, Labor, and Pensions Committee will please come to order. Today, we are having the second of two hearings on reauthorizing four Food and Drug Administration user fee programs. I will have an opening statement, followed by Ranking Member Burr, and then we will introduce our witnesses.

After the witnesses give their testimony, Senators will each have 5 minutes for a round of questions. And while again, while we were unable to have this hearing fully open to the public or media for in-person attendance, live video is available on our Committee website at *help.senate.gov*. And if you are in need of accommodations, including closed captioning, you can reach out to the Committee of the Office of Congressional Accessibility Service.

Before we discuss the importance of the user fee programs to FDA's drug and device work, recent reporting has put a spotlight on issues with the FDA's food, safety, and nutrition efforts, including several that have frustrated me for a long time.

While some important steps on nutrition and safety have been stalled for years, we have also seen more recent threats met with a frustratingly slow response, like arsenic and other heavy metals in baby food or contaminated infant formula, which FDA first received complaints about last September but was only recalled earlier this year.

I am going to keep pressing for answers from FDA leadership on how they will end the pattern of delay and dysfunction here, be-

cause FDA's mission, when it comes to ensuring our food is safe and healthy, is too important to be on the agency's back burner. Because people in Washington State and across the country depend on the FDA doing its job quickly and carefully every single day in more ways than even they realize.

Whether they are getting a meal or a prescription or an ultrasound or almost anything in between, they are putting the well-being of themselves and their families in FDA's hands. We owe it to them to make sure the FDA has everything it needs and is doing everything it can to live up to that huge responsibility.

The user fee programs have an important role to play when it comes to FDA's work ensuring the safety and effectiveness of medical products families rely on to stay healthy. These programs make sure that as FDA gets more new drugs or devices to consider for approval, and as it gets more critical work to do, it also gets more resources to support that work.

Given the importance of these programs for keeping families safe, Congress has regularly reauthorized them in a bipartisan way, and I am glad to be working with Senator Burr and our colleagues on this Committee to get this done once again in a timely manner. Because it should be unthinkable that after 2 years, when lefties work has become more important than ever, we would fail to get this done or force the agency to send pink slips. But it should also be unthinkable that we would let this moment slip by without looking carefully at what is and is not working at FDA.

That starts with looking back at this pandemic, from FDA's incredible work to quickly review and approve safe, effective vaccines, to the challenges it faced like misinformation and political interference from the previous administration, to other issues we saw, like the constant struggle with testing shortages, the hydroxychloroquine debacle, and the ongoing frustration parents are dealing with because of unclear timelines for vaccines for young children, which I am expecting to hear answers about at today's hearing.

We need to learn from these challenges, something Senator Burr and I have already started to work on in our Prevent Pandemics Act. But we need to look beyond this pandemic as well, because there are countless issues right now that families in Washington State are struggling with, but which FDA is struggling to address. We have to make sure the approval process works for families, not just pharmaceutical companies' bottom lines, and that patients are having their voices heard and concerns addressed by FDA.

That means better steps to ensure drugs work for everyone, such as increased diversity in clinical trials and pediatric drug research and means ensuring the accelerated approval pathway benefits patients. And it absolutely means lowering drug costs that have been skyrocketing for years and leaving patients with impossible choices. Which is why I want to cap insulin costs at $35 a month.

It is also why I want to take steps so FDA can do more to bring down barriers that block cheaper generics and biosimilars from getting to market and stop pharmaceutical companies who game the FDA system to block competition from cheaper drugs. I also want FDA to make good on the promise of a law we worked in this Com-

mittee to pass half a decade ago. And finally, let hearing aids be sold over-the-counter and at lower cost to millions of people.

There is no good reason we are still waiting for FDA to implement this step and save millions of people thousands of dollars. We also need to be looking at what more we can do to address substance use disorders and the opioid crisis, as overdose deaths keep setting record highs and fentanyl is wreaking havoc in our communities. And while there is clearly more we can do to strengthen the FDA's oversight of drugs and devices, there is also an alarming number of products that currently get no meaningful oversight.

When it comes to cosmetics, we have discovered known carcinogens like asbestos and formaldehyde in baby powder, children's makeup kits, and hair products. And when it comes to dietary supplements, people across the country are faced with a shelf full of products that make health claims but lack oversight.

FDA does not have the authority to collect basic information about these products or even to know what is on the market. People buy, use, and entrust their health to these items every day, and they deserve to know these products are safe, vetted, and subject to careful FDA oversight. So I hope we will be able to make progress on all of these issues and more as we work to reauthorize the user fee programs.

I look forward to hearing from our witnesses today about these challenges, thank you for being here, and to working with my colleagues on both sides of the aisle to address them in a bipartisan way. And as we look at how to support FDA's work, I hope we can also make progress soon on the urgently needed funding for our COVID response.

We have got to get that done because families are counting on us to provide communities the tests, treatments, and vaccines they need to keep people healthy, protect our hard won progress against this pandemic, and keep our Country ready for whatever comes next.

With that, I will turn it over to Ranking Member Burr for his opening remarks.

OPENING STATEMENT OF SENATOR BURR

Senator BURR. Thank you, Madam Chair. And if I could take a point of personal privilege for a moment, I want to reflect on the passing of Senator Orrin Hatch. When the Reagan revolution came to the Senate, Orrin Hatch became the Committee's Chair. He was a remarkable Senator and a good friend to many of us on this Committee. His work in this Committee and others is something we should all be proud of. Without Orrin, we wouldn't have a generic drug industry. Think of how many lives have been saved because of that and how many billions have been saved with lower cost drugs.

He was also the author of the Americans With Disabilities Act, helping improve the lives of millions of Americans with disabilities, giving them opportunities and freedoms to live quality lives. The list of what he accomplished could go on and on.

I am saddened by his passing, and my heart and prayers go out to his beloved Elaine and their children, and to his friends and the staff who worked for him because I know they are hurting today as well. And I thank the Chair.

Madam Chair, I thank you for holding this second hearing today on FDA's user fee program, and for working with my staff and me on policies that have the potential to go along with the legislation as we reauthorize them. The user fee reauthorization provides one of those rare opportunities in Congress for true bipartisanship and should be seen as a time to take a hard look at the policies that affect the daily lives of the American people.

I would bet that each person watching or participating in this hearing has already used several products today that are regulated by the FDA. That is why it is so important for the agency to keep pace with the advancements in these products that they regulate. If today's hearing had a theme, it would be accountability. You are here today to be held accountable to the Congress and to the American people.

During COVID–19 pandemic, FDA leveraged its authorities and responded swiftly to help private sector partners develop and bring test, treatments, and vaccines to the American people in record time. I was thrilled that the agency embraced the letter, and more importantly, the spirit of the law. But this seems to be the exception, reserved for emergencies, and not the rule.

COVID was a crisis and you acted fast. But a diagnosis of cancer or Alzheimer's is also a crisis for families facing that news day in and day out. The agency needs to apply practices that used during COVID response to its everyday operations to help speed not only the review of products, but their development as well. Why shouldn't we expect you to treat more things with the same urgency you applied to the pandemic?

We learned during the pandemic, FDA has a fractured framework for clinical tests. It has blind spots where some of the most important tests for patients and their doctors are concerned, like genetic tests. I want to work on updating FDA's regulation for diagnostic tests, and in working with the Chair to update the regulations of other products like cosmetics and dietary supplements.

I am glad the Chair's interested in rolling up her sleeves and joining with me on this. But there is an elephant in the room. The FDA has a responsibility to meet the terms of the commitments it has made under the user fee programs. Based on my evaluation, you have not fully delivered. During the last two decades, I have legislated major reforms at FDA across almost all of its programs. The 1997 user fee bill was my bill for FDAMA.

It brought needed reforms to streamline drug review, establish risk based regulation of medical devices, and required the agency to be more flexible with types of evidence it considered for the products it regulates. In 2010, I worked with Senator Judd Gregg, Ted Kennedy, Lamar Alexander, and others to write the Food Safety Modernization Act aimed at reducing food borne illnesses and deaths and modernizing the food safety programs at the agency.

In 2012, I worked with Tom Coburn to hold FDA more accountable, reduce product review times, address cultural changes at the agency to reinforce that review speed matters, especially to patients with a ticking clock. In 2013, this Committee worked to provide regulatory certainty for compounded drugs, and I worked to ensure the agency had the track and trace authorities it needed to improve its ability to detect unsafe, counterfeit medicines.

However, I have also been the roadblock to many proposals when I feared that the agency was not ready for the role Congress wanted it to play or the mission was at risk. I have also objected to giving FDA new and expanded authorities that, quite frankly, I didn't think they should have, especially when FDA fails to address my concerns about accountability.

I fought against the passage of the 2009 tobacco law because I knew the FDA didn't have what it takes to regulate these products. Safe and effective applies everywhere in the FDA except CTP. It should have been at ATF all alone. 13 years and more than $7.5 billion and its authorized only one vapor product, only one. Only one potentially less harmful alternative for lifelong smokers.

I held the 2012 user fee bill on the Senate floor and spoke for hours to run through my longstanding concerns with the user fee programs and the FDA posture that a user fee bill could be dropped in the lap of the U.S. Senate and passed without question. I fought to uphold FDA's gold standard of review, including when other agencies thought they could perform FDA's function better.

I deeply value and believe in the mission of the Food and Drug Administration, which is why the commitments that FDA makes are so important and the goals it misses are so concerning. The user fee legislation that will come before this Committee for a vote in just a few weeks must hold the FDA accountable for its actions and inactions. Accountability is not an option. You don't get to set goals you can't meet and pretend that is accountability. Each of the new agreements this Committee is evaluating reflect major new commitments, more money, more staff, more Government.

But what we do about previous commitments that went or remain on—what do we do with commitments that went or remain unfulfilled? For the drugs program, in Fiscal Year 2019 and 2020, FDA missed 12 out of the 14 user fee goals in the new drug program related to product development meetings with sponsors, leaving the innovators in limbo. Meeting 2 of 14 goals is a 15 percent success rate.

I believe that would pretty much be an F by anybody's grading curve. For the biosimilars program, in Fiscal Year 2020, FDA only reviewed 50 percent of the applications on time, and FDA missed 7 out of 15 goals related to biosimilar product development meeting. I am quoting you the facts here of things that you committed to do, not Congress imposed on you.

50 percent of 7 out of 15, that would also be an F under anybody's grading. And for the medical device program, not only will FDA be 3 months late in finalizing the agreement, it took so long because it refused to acknowledge that the agency didn't meet all of its goals from the last round.

Now FDA wants double the money for mediocre performance improvements, and for certain devices, longer review times. But the missed commitments don't stop there. Missing explanations on deficiency letters, a carryover balance the size of a whole year of user fee, and the failure to finalize guidance critical to some of the most important advanced products in the field.

More money, lower expectations of accountability, no accountability for past failures, and on top of this, a new, costly program aimed at shepherding certain devices through the review process for which FDA has zero clear deliverables, when you already essentially have this authority because I have already given it to you. And you expect Congress to rubber stamp these agreements? My friends, I don't think so.

After two transformative, challenging years at FDA, I know you can do better. The American people saw you do better. And you have an opportunity today to convince me that the agency is on the right track for patients. The more you use the user fee process to bully dollars out of an industry, holding them hostage in the negotiating room, the less accountable FDA is to the American people and their elected representatives, period.

American patients deserve user free programs that bring medicines to them on time, that keep pace with technology, that reduce the time and cost of development and treatment, and that do not grow just to put more Government in between patients and cures. I come to this process as a good faith partner to my colleagues and as long—as a long standing advocate of the FDA, but not as a doormat.

This Committee has never shied away from difficult FDA policy discussions. I promise this process will be thorough and critical, so that the agency can rise to the challenge of the next generation of scientific advancements to improve the lives of the American people. I know you can do it.

With just a little more accountability added to these programs, I am optimistic that my colleagues and I will be able to get these agreements signed into law. But if there is more—if there is not more accountability, I see no reason why I shouldn't stand in the way.

Madam Chair, I thank you.

The CHAIR. Thank you, Senator Burr. And thank you for beginning with a tribute to Senator Orrin Hatch. Those of us who served with him remember his tremendous contributions to this Committee, to this Country, to the people of America.

My condolences as well go to his family, his friends, and his staff, and everyone who knew him and didn't know him because his legacy will live on. So thank you. Thank you for that. I will now introduce today's witnesses. Our first witness today is Dr. Patricia Cavazzoni. She is Director of FDA's Center for Drug Evaluation and Research. We will also be hearing from Dr. Peter Marks. He is the Director of the Center for Biologics Evaluation and Research.

Our final witness is Dr. Jeffrey Shuren. He is the Director of the Center for Devices and Radiological Health. Thank you all for

being here with us today to share your time and expertise, and I look forward to hearing from each of you.

Dr. Cavazzoni, we will begin with your testimony.

STATEMENT OF PATRIZIA CAVAZZONI, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, UNITED STATES FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. CAVAZZONI. Thank you, Madam Chair, Ranking Member Burr, and Members of the Committee. I am Dr. Patricia Cavazzoni, Director of the Center for Drug Evaluation and Research at the FDA.

I appreciate the opportunity to appear before you today, along with my colleagues Dr. Marks and Dr. Shuren, to discuss reauthorization of the user fee programs covering brand name drugs, generic drugs, biosimilars, and devices. We appreciate the efforts of Congress, and this Committee in particular, in reauthorizing these programs in previous cycles, and look forward to continuing our partnership this year.

Dr. Marks will speak about PDUFA in his testimony, I will focus my opening remarks on the generic drug user fee program, or GDUFA, and the biosimilar drug user fee program, or BsUFA. These programs have allowed FDA to provide access to affordable, high quality medicines to millions of Americans who otherwise couldn't afford them.

Since its creation more than 10 years ago, GDUFA has allowed the agency to approve thousands of generic medicines, resulting in significant cost saving for consumers. By some accounts, generic drugs saved the U.S. health care system more than $2 trillion over that period. Patients' confidence that generic drugs will work the same as brand products and can be freely substituted is the foundation for the access and savings that generics have produced for the health care system.

We intend to build on this success by approving more drugs in a single round of review, including complex generics with little or no competition. With more generic drugs on the market, there is a corresponding increase in the need for FDA advice over the lifecycle of these products. Indeed, we see a steady increase in generic drug applications with post-approval actions.

In addition, as brand name drugs become increasingly sophisticated and harder to manufacture, the generic program faces increased demand to keep up with innovation. GDUFA III would introduce new measures that allow for earlier approvals and will ensure that the agency has the appropriate staff expertise to deliver on our goals year after year. Let me now turn to the biosimilar user fee program, or BsUFA.

The abbreviated biosimilar approval pathway saves the developers time and resources, thus encouraging competition and potentially lowering health care costs. Since the enactment of BsUFA II 5 years ago, the number of approved biosimilar products has grown from 5 to 35 today, including an interchangeable insulin product.

BsUFA III proposes to retain the majority of existing review performance goals, with changes to some of the meetings between FDA and developers to improve communications. With a growing portfolio of approved biosimilar products, the proposal seeks to expedite the review of new indications or other changes after the initial approval.

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

To close, I cannot emphasize enough the critical importance of reauthorizing these three user fee programs. Without them, FDA's medical product programs, which have allowed for hundreds of treatments and cures for life threatening diseases, would not exist as they are today.

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

As the BsUFA program continues to grow, we anticipate that it will complement GDUFA by expanding the availability of even more high quality, affordable medicines for all those who need them. Thank you again for the opportunity to be here today. I look forward to your questions.

[The prepared statement of Patrizia Cavazzoni can be found on page 31 in Additional Material.:]

The CHAIR. Thank you.

Dr. Marks.

STATEMENT OF PETER MARKS, M.D., PH.D. DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, UNITED STATES FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. MARKS. Chair Murray, Ranking Member Burr, and Members of the Committee, I am Peter Marks, Director of the Center of Biologics Evaluation and Research at the Food and Drug Administration. I am pleased to be here today with my colleagues to discuss the reauthorization of the medical product user fee programs. For my portion of the testimony, I will focus on the Prescription Drug User Fee Program, or PDUFA.

Both CBER and CDER will implement the commitments contained in the PDUFA commitment letter, which will refer to its PDUFA VII. So, know that while I am presenting the elements of the PDUFA VII letter, both Dr. Cavazzoni and I share the responsibility for oversight of the program.

Since first enacted 30 years ago, PDUFA has revolutionized the United States drug approval process. It has reversed the lag in drug approvals that prompted its creation, providing Americans with more timely access to safe and effective medical products. Today, almost two-thirds of new active substances approved globally are first launched in the United States.

It is not an understatement to say that there are many people with us today who would not be here without the program, which has dramatically reshaped drug development and approval in the United States, bringing potentially lifesaving medical therapies to patients in a much more timely manner.

Though it began with a general focus on shortening review times, through successive 5 year PDUFA reauthorizations, program enhancements have evolved and expanded significantly. Enhanced interactions give us the opportunity to provide more guidance to sponsors, improving the potential for first cycle approvals and getting safe and effective drugs to patients sooner.

These interactions also enable sponsors to incorporate the advances in regulatory science into their development programs, expediting drug development and facilitating timely regulatory interactions and decisions. Reauthorization of PDUFA will enable the agency to collect fees to support the review of new innovative drugs.

The PDUFA VII commitment letters' focus includes the following categories, among others, it will enhance CBER support for development, review, and approval of cell and gene therapy products and new allergenic extract products, advance—apply scientific research to expedite drug development, it will continue the enhancement and modernization of the drug safety system, advance the utilization of innovative manufacturing technologies, and improve FDA's hiring and retention of key scientific and technical talent.

As the Director of CBER, I would like to direct your attention for a moment to the PDUFA VII commitment focused on new enhancement to CEBR's support for the development, review, and approval of cell and gene therapy products and new allergenic extract products. FDA has experienced exponential growth in cellular and gene therapy submissions over the past 7 years, with close to 2,000 active development programs.

We have seen a sustained increase in development program activities, including an 85 percent increase in investigational new drug applications and a 158 percent increase in formal meeting requests.

A number of these programs, such as regenerative medicine advanced therapy, or RMAT designation, which was enacted by Congress as part of the 21st Century Cures Act, have the potential to bring new therapies to meet unmet medical needs for serious and life threatening conditions.

Since December 2016, 72 of 187 requests that have received RMAT designation—have received RMAT designation, with three of these designated products having received approval in 2021. These include two allogeneic cellular products, one for children with a rare immune disorder, one for wound healing, and a CAR-T cell therapy for patients with a kind of cancer B-cell lymphoma.

To meet the demands of the rapidly expanding cell and gene therapy portfolio, PDUFA VII proposes new enhancements to CBER's capacity. The proposal will allow the agency to produce multiple guidances, to host public meetings to examine new technologies and approaches, and to better understand patient perspec-

tives on gene therapy products, and to conduct public outreach to facilitate product development and approval.

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

The enhancements of cell and gene therapy and allergenics are just two examples of the important enhancements proposed under PDUFA VII, and we will be happy to answer questions regarding the others. Thank you for your time today.

[The prepared statement of Peter Marks can be found on page 31 in Additional Material.:]

The CHAIR. Thank you. Dr. Shuren.

STATEMENT OF JEFFREY SHUREN, M.D., J.D., DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, UNITED STATES FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. SHUREN. Chair Murray, Ranking Member Burr, Members of the Committee, thank you for the opportunity to testify today about the fifth reauthorization of MDUFA. The investments made in previous MDUFA authorizations have paid dividends, as we continue to see an increasing number of innovators bringing their devices to the U.S. first, and a more robust pipeline of innovative technologies.

I want you to know that I personally regret that we missed the statutory deadline to deliver our recommendations to Congress, an obligation that I and the entire agency take seriously. I am pleased to report, however, that the long deliberations that ultimately produced a strong, thoughtful agreement on recommendations to Congress that, if enacted, will continue to advance medical device innovation, while increasing accountability for the program, and maintaining the FDA's standards to protect patients.

CDRH continue to meet and exceed most performance goals through the first half of MDUFA IV. However, we missed some goals later on. During this time, we saw a rise in our workload for which we were not fully funded. For example, so far during MDUFA IV, we received over 3,000 more pre-submissions than we were resourced to review.

The number of breakthrough device designations we have granted has increased by almost 60 percent. Medical devices have and continue to be increasingly more complex, and the review of their premarket submissions, more resource intensive. While the number of submissions we receive annually has increased as well, and we expect these trends to continue. And then COVID hit.

It pushed us into a continuous all hands on deck operation in order to facilitate the development and availability of pandemic related medical devices. CDRH has received over 8,000 emergency use and pre-EUA requests, and we are still receiving about 120 of these submissions a month. We have granted emergency use for

full marketing authorization to nearly 2,300 medical devices for COVID–19, including over 460 tests and self-collection kits.

This has truly been a perfect storm that my center has been battling against for over 2 years. Moreover, our efforts to grant EUAs are not covered under the scope of MDUFA, and they don't count toward that performance. On the other hand, the magnitude of the emergency response inevitably led to a backlog and delayed review times, and we fell short on some of our MDUFA IV goals.

We know this has had a great impact on companies across the country. This is why we have been transparent, communicating about impacts publicly and regularly, and we have worked hard to address delays for COVID and non-COVID devices through hiring more staff and contractors, reallocating current staff, and changing policy procedure and practice, with many of my staff burning the midnight oil and burning out in the process.

We greatly appreciate the support from Congress, particularly in the form of supplemental funding, and we have now turned the corner. We have already reduced the backlog of non-COVID device submissions by 45 percent, and we are targeting to have most of the center back to normal operations by later this year.

Despite these challenges during MDUFA IV, we continue to authorize record numbers of novel devices, over 100 a year, even during the pandemic. And we granted almost 600 breakthrough device designations, with most designations going to small startup companies. Even while falling short of some goals and facing our most challenging year to date, we have continued to provide value to innovators and to patients.

The MDUFA V proposal takes important steps to address resource gaps that began to show before COVID–19 and to support improved performance. It also features many new accountability mechanisms, one of which is for add-on payments under which FDA would receive additional user fees if it meets specified goals.

These additional funds come with even more ambitious goals for the later years MDUFA V. The agreement includes a new voluntary pilot, TAP, to provide earlier, more frequent, and more strategic engagement with sponsors of breakthrough designated devices and those included in the Safer Technologies Program to speed device development, and we will be tracking over half a dozen metrics for devices in the pilot to make sure that TAP provides a return on investment.

The initiative is another way we are continuing to incorporate lessons learned from the pandemic, where we saw how engaging with sponsors through the pre-EUA process to problem solve and answer their questions in real or near real time was critical for facilitating important technologies coming to market quickly and safely.

The MDUFA V proposal would also support advancing the patient perspective in regulatory decisions, expanding the use of consensus standards, leveraging real world evidence for regulatory decisionmaking, and advancing global harmonization, among other priorities. We appreciate Congress's patience and support.

Thank you again for the opportunity to testify today.

[The prepared statement of Jefferey Shuren can be found on page 31 in Additional Material.:]

The CHAIR. Thank you very much to all of you. We will now begin a round of 5 minute questions. And I again ask my colleagues, keep track the clock and stay within those 5 minutes. Dr. Mark, I want to start with you. Families are still waiting for a COVID vaccine for children under the age of five. And this week there were reports that they may be waiting till June.

Throughout my state, I have had parents talking to me about this. They are frustrated, they are confused, and I am, too, and they really do deserve some clarity on this.

For parents back in my home of Washington State, across country, can you tell us when you expect a COVID–19 vaccine for young children and why it is taking so long, and what we need to know in the meantime to keep children safe?

Dr. MARKS. Thank you, Chair. Once we have a fully complete emergency use application, we will move quickly, without sacrificing our standards, to finish our evaluation of COVID–19 vaccines for children under 5 years of age. It is one of our highest priorities, and we care very deeply about the health and well-being of children. But simply making a vaccine available doesn't matter if parents don't get their kids vaccinated. So it is critically important that we have the proper evaluation so that parents will have trust in any vaccines that we authorize.

As we work to complete our reviews, we will bring the vaccines before independent advisers to have a discussion of the data. And if we authorize the vaccines in young children, parents will be able to have access to the information that they need to be confident in making their decisions on vaccination.

We are deeply committed to getting a safe and effective COVID–19 available for all children, and we will make sure we get the job done and get it done correctly. In the next week, we will make public a tentative timeline for advisory committee meetings for several expected applications.

But just remember that we can't actually finish our reviews until we actually have complete applications in the FDA.

The CHAIR. So are the—we don't have complete applications, is that why this is taking so long?

Dr. MARKS. You know, unfortunately, we can't comment publicly on the state of this, but I would direct you to the fact that the manufacturers generally will make an announcement when they have a full and complete application in with us for emergency use.

But you can surmise what the situation is because we will proceed with all due speed once we have complete applications. Some of these are complicated because they are relatively larger, covering larger swaths of the pediatric population than others.

The CHAIR. Dr. Cavazzoni, when it comes to opioids, we have seen how FDA failures in the past have really contributed to a nationwide crisis, and that continues to tragically grow for families and communities across the country. Last year alone, we lost over 100,000 people to drug overdoses. That is a heartbreaking record.

More and more of these deaths are due to fentanyl. Fentanyl overdose deaths in my home State of Washington have increased tenfold in the past 6 years, which is a stunning increase. And we really do need an all hands on deck effort to do everything possible to get our handle on this problem and save lives. And that includes FDA taking decisive action to respond to the fentanyl crisis.

FDA was too slow and too hesitant to address this in the past, and I think every Member of this Committee really believes we need to be more aggressive and dynamic steps need to be taken now and going forward. So while you are here, I want to ask you, what is the FDA doing to aggressively work with Federal partners to address the use of illicit fentanyl related substances and expand access to high quality treatments for opioid use disorder and overdose reversal drugs that can save lives like naloxone?

Dr. CAVAZZONI. Thank you, Madam Chair. The efforts to fight the opioid epidemic are—really need to—FDA as well as all our Federal partners, because it is a very complicated situation.

We are redoubling our efforts when it comes to fighting the opioid epidemic, looking at all potential tools that we have. And for instance, very recently we have issued a Federal register notice indicating that we are considering including mailbag envelopes in—with prescriptions as part of the opioid grants.

We are also very, very focused on expanding the access of naloxone. Any particular OTC and naloxone, we understand the need. We stand ready to work with manufacturers to expedite the review of these products so that we make opioid reversal agents more broadly available to the American people.

The CHAIR. Okay, thank you. And my time is expired. I do you have additional questions, but I will turn to Senator Burr.

Senator BURR. Thank you, Madam Chair. Dr. Cavazzoni, in the last PDUFA agreement, FDA committed to 230 new hires by Fiscal Year 2022. According to the FDA's Performance Report for Fiscal Year 2021, it has hired 212 of those new hires.

Yet there are currently a total of 260 PDUFA funded vacancies across the Drugs and Biologics Center. Here is my question, how can the FDA say that it has met its hiring commitments with so many underlying vacancies in the PDUFA program? And why does FDA not account for net employment?

Dr. CAVAZZONI. Thank you, Senator, for that question. When we look at the vacancies that we have in place, it is important that we put them within context of our total number of staff in the user fee program. And so our current vacancies represent approximately 7 to 8 percent of our total staff. And this is not an unexpected rate of vacancy or attrition in large organizations. It is also important to keep in mind that when an employee leaves, we immediately start the process to backfill that position.

If you look behind those vacancies, they have activities behind them to bring them on board. We are overall on track to meet our hiring commitments by the end of the cycle. And yes, we are asking for additional personnel as part of the next authorization cycle. And it is important to keep in mind that the additional personnel are really meant to support the incremental activities and commit-

ments that we have negotiated with industry, and that the current personnel, including those backfilled vacancies, have—are really there to meet our current commitments.

We work very, very fast to try to backfill those open vacancies, utilizing the tools that Congress has given us, for example, 21st Century Cure hiring authority, which has been very, very helpful to us.

Senator BURR. I think it has been helpful. And Dr. Cavazzoni, I have been here for 28 years, but I still don't buy into the belief that if you have hired 212 people under the commitment, but you have 260 vacancy, I as an applicant should feel good about that. That tells me that there are less people working on application, work in the entire division. So maybe we will have a disagreement there. But I certainly understand why the industry looks at this and says, well, technically you may have reached your goal, but if you actually have less people working in the PDUFA than you did when we started, so it is a net loss.

Dr. Shuren, the pandemic highlighted the fragmented approach for our Country to take to—takes to diagnostic test regulations. I have been working for more than 3 years together with a new proposal, the VALID Act, to reform the way we regulate test and encourage innovation in the field. Do you agree that our approach to clinical tests needs to be reformed?

Dr. SHUREN. I do. We are supporters—and first of all, I just want to thank you and Chair Murray for your leadership on trying to drive diagnostic reform. And we are very supportive of having reform, working with you on the final product. What that has to be, though, is to make sure that it covers all tests. Doctors and patients don't care who makes your test, they just care that your test works.

Senator BURR. Jeff, you said a minute ago, we are trying to be transparent, so let me just be candid. By law, meeting minutes for MDUFA negotiations are required to be posted publicly before the agreement is transmitted to Congress.

Today, there are no meeting minutes from any meeting since February of this year. You posted minutes for nine meetings between September and February over the weekend. We are still missing the minutes from seven meetings. Congress—well, will you commit to publish 100 percent of the meeting minutes before finalizing the commitment letter?

Dr. SHUREN. Yes. We are hoping to have all the meeting minutes through March 7th posted today.

Senator BURR. Why has that been so difficult? Just out of curiosity.

Dr. SHUREN. Out of curiosity—you know what, it is a negotiation in and of itself with the industry parties. And you have seen how those negotiations go, a lot of diverse opinions. And the big focus was trying to get the deal done, get the meetings afterwards. We agree with you. It is hard for you to make informed decisions without those meeting minutes present.

I think we and industry both struggled with the resources available with COVID as well. So we see this as an unusual cir-

cumstance, and we know this is not the way going forward. We will have the rest of the meeting minutes out by the end of this week. And we are targeting to have the final package to you all by the end of next week.

Senator BURR. Thank you, Madam Chair.

The CHAIR. Thank you.

Senator Hassan.

Senator HASSAN. Well, I want to thank you, Madam Chair and Ranking Member Burr, for having this hearing. And thank you for the witnesses for being here today. Dr. Cavazzoni, last summer, I led a bipartisan letter to the FDA, raising concerns about the apparent conflicts of interests surrounding the consulting firm McKinsey. The firm worked for the agency on opioid related projects while also simultaneously working for opioid manufacturers like Purdue Pharma.

The FDA's response to the letter indicated that McKinsey failed to disclose any potential conflicts of interest when applying for FDA contracts. And earlier this month, Chair Murray and I led a letter asking the HHS Inspector General to investigate further. What actions is the FDA now taking against McKinsey based on the firm's failures to disclose apparent conflicts of interest?

For example, is the FDA's suspending current and future contracts with McKinsey and referring this case to the Department of Justice for potential violations of the False Claims Act?

Dr. CAVAZZONI. Thank you, Senator, for that question. It is very important to establish that while McKinsey have I work with FDA under contract for over several years, their work did not entail specific regulatory work or a scientific review work pertaining to products or product classes.

Senator HASSAN. But my question is, what are you doing to make sure that we don't come to a place like this again, and to hold McKinsey accountable for failure to disclose what is an apparent conflict of interest?

Dr. CAVAZZONI. So FDA follows the U.S. Government contracting rules, and those rules require contractors to disclose any conflict of interest. And we expect contractors to do so. So this is the framework under which we operate, and we will continue to set those expectations.

Senator HASSAN. So I am going to follow-up with you additionally, because I am still interested in wanting an answer to whether you are going to suspend contracts, current or future contracts with McKinsey. Whether there is a case for referring this to DOJ. And I will continue to follow-up on the issue, including with the HHS Inspector.

Dr. CAVAZZONI. To orient you to that—the Center for Drugs currently does not have a contract with McKinsey. And across FDA, the—we anticipate that certain contracts will not be issued pending the outcome of the investigations. And I can defer to my colleagues, Dr. Marks, to speak to CBER.

Senator HASSAN. Well, I am going to hold off on that because I have a few other questions and limited time. But I will follow-up with you, Dr. Marks. I have another question. Dr. Cavazzoni. In

the FDA's response to my original letter, the agency claimed that it first became aware that McKinsey had taken on opioid manufacturers as clients in early 2021.

However, the New York Times reported on McKinsey's representation of Purdue Pharma in February 2019. Contracting data bases show that from February 2019 to January 2021, McKinsey received more than $20 million in new contracts from the FDA. How did the FDA fail to notice McKinsey's apparent conflicts of interest until almost 2 years after they were public knowledge printed in the New York Times?

Dr. CAVAZZONI. As I mentioned earlier, we rely on Government contracting rules which set the expectations for contractors to disclose conflicts of interest. And it is also very important to highlight that the work that McKinsey did at FDA was about general process, concept of operations, organizational design, and did not entail involvement, direct involvement in product regulation or scientific review.

Senator HASSAN. That may or may not be true, but the reality is that when somebody who is bragging to drug manufacturers that they know what questions to ask and have influence at the FDA, that should be of concern. And it strains credulity to think that nobody at the FDA involved with McKinsey between 2019 and 2021 had any idea that the company had major potential conflicts of interest based on news reports in major publications.

How is the FDA adjusting its contracting processes going forward to ensure that it is aware of publicly reported information about apparent conflicts of interest with major companies to which it is awarding tens of millions of dollars in contracts?

Dr. CAVAZZONI. As I indicated earlier, we follow contracting regulations that apply across the entire U.S. Government, including other agencies. And we rely on contractors to follow those rules and to inform us of any conflicts of interest.

Senator HASSAN. I appreciate that answer. I think it is not sufficient for us to rely on self-reporting anymore. And I look forward to working with Members of committees on whether we should exclusively rely on self-reporting from contractors, given what we have seen from McKinsey. Thank you, Madam Chair.

The CHAIR. Thank you.

Senator Cassidy.

Senator CASSIDY. Dr. Cavazzoni, I introduced legislation with Dr. Smith that would consolidate the process for FDA to make therapeutic equivalence determinations for 505(b)(2) new drug applications. What data does FDA need to make a therapeutic equivalent determination, which is not otherwise included in the 505(b)(2) application?

Dr. CAVAZZONI. Thank you, Senator. And we are aware of that legislation, and we understand and agree with the importance of the therapeutic equivalence evaluations as a means to allow a substitution of drugs at the pharmacy. The pathway that we have to generate data that supports a therapeutic equivalence application is the generic drug review pathway. It is really fit for purpose to

provide that answer by the time—at the time an application is approved.

When—conversely, the 505(b)(2) pathway is really not set up to generate the data that by the end of the review of the application or even after the application has been reviewed, would allow us to make a determination of therapeutic equivalence. Why? Because the review tools and the actual regulations are really not set up to yield those data by the time the 505(b)(2) application is reviewed.

We are concerned that requiring a proposal to require that therapeutic equivalence evaluation be done within the context of 505(b)(2) applications would be very difficult to implement under the current framework.

We are interested in better exploring any barriers in the generic drug review program that may make it more difficult for some of these applications to come through the generic program where we can make those determinations very efficiently.

Senator CASSIDY. Thank you. Doctor—either Dr. Cavazzoni or Dr. Marks, there has been a recent court ruling that has called into question some aspects of the Orphan Drug Act. Specifically, courts have determined FDA can only award orphan drug exclusivity for an entire condition as opposed to indications within a condition.

Can you elaborate on how this change in the scope of orphan drug exclusivity would impact current and future patient access to generics and biosimilars?

Dr. MARKS. Thanks, Senator, for that question. So that particular decision has particular implications on the development of drugs, particularly in the pediatric realm for pediatric rare diseases. With orphan drug exclusivity, one does not necessarily have to develop a drug for a pediatric population with this decision now. In the past, there would be a separate population that could have been granted for the pediatric population, allowing development to occur both in the adult orphan population and in the pediatric orphan population.

With this, that pediatric place is blocked. We view that as a potential problem for the development of drugs for rare diseases. And we would very much look forward to working with Congress to try to find a solution to this issue.

Senator CASSIDY. To the point on it, working with Baldwin and Cassidy, because we are the ones who have the bills, just to say that, Madam Chair, Mr. Ranking Member. Dr. Shuren, Congress has previously directed that the FDA issue certificates to foreign governments for FDA approved medical devices that are exported from an FDA registered establishment outside of the U.S..

However, instead of doing that, I am told, in 2020, FDA established a new form of certificate known as the certificate for device not exported from the United States. And this is, as I understand it, explicitly says that the FDA has not—does not convey that it would be lawful to import the market—or market the device in the United States.

The FDA is the gold standard, this is unnecessarily burdensome language, so it seems, and has caused confusion among manufac-

turers and foreign regulators. Congress asked you to do this and you have not done it. Can you comment on all this?

Dr. SHUREN. Well certainly. There are two different situations. The certificate for foreign government is where we have a device that is made in the U.S. that has been exported to another country. It is subject to requirements in the U.S. like oversight on the manufacturing.

The FDA is in a different position to provide assurances regarding that device. Under the new provision, these are devices that are made in another country, and they are sent to a different country. They are not in the U.S..

They are not subject to the U.S. requirements. The FDA hasn't overseen them. We can't make the same assurances, and we do not want to convey to a foreign government something that would be incorrect. That said, there may be ways to fix this. There are some Members in the House who are interested in doing so.

If there is interest in the Senate, we would be interested in working with you or other Members to go ahead and do that.

Senator CASSIDY. May I have a follow-up question? I am told, though, that these are devices manufactured in facilities, and these facilities export these devices into the United States. Presumably that means the facility would then have been inspected by FDA.

FDA does not allow devices to be imported unless they have inspected the facility. So I have I been told incorrectly that FDA has not inspected these facilities and has not approved these devices for sale within the U.S.?

Dr. SHUREN. Well, for devices that are made overseas, and they are not for the U.S. marketplace, we would not have reviewed——

Senator CASSIDY. That is not what I am asking you.

Dr. SHUREN. Yes——

Senator CASSIDY. If there is a device from a facility, and that facility is approved to send the device into the U.S., that same facility is sending the same device to another country. That is my understanding of the current circumstance and that for which a certificate for foreign government was directed by Congress to be issued. Now, is my understanding of this situation incorrect?

Dr. SHUREN. If that device, sometimes when you deal with a device that is made on a different manufacturing line for another country, that goes——

Senator CASSIDY. Again, I am not saying that. It is the same device brought to the U.S. that is then being sent to another country. And so same manufacturing lines, same device, it is just going in two different directions. And I think that was Congress's intent.

Dr. SHUREN. And that is a point where we think we could deal with clarification and then allow for those circumstances.

Senator CASSIDY. And so your point is, it is not clear in what Congress previously passed that has that specificity?

Dr. SHUREN. That has been my understanding. But I would be happy to get back to you on that.

Senator CASSIDY. Thank you. I yield. Thank you.

The CHAIR. Thank you. Senator Baldwin

I am sorry, Senator Rosen.

Senator ROSEN. Well, thank you, Chair Murray, Ranking Member Burr, for holding this important hearing, for our witnesses, for your service and participating today. And speaking with bills with partners, Senator Cassidy and I have quite a few bills too. I am going to talk about one of them right here, because as we have discussed previously, cyberattacks, of course, are a growing threat to our health care sector.

Senator Cassidy and I have just introduced legislation that improves collaboration among agencies to bolster protections for the medical field. So as we work to strengthen protection for our health system, we must also provide protections for all the way down to these medical devices.

To address this, I am working on additional legislation to ensure cybersecurity guidance for medical device manufacturers. We want that guidance to be up to date and nimble so that Federal resources through CISA, they are easy to understand and easy to access for health care providers. So Dr. Shuren, the current FDA guidance for medical device cybersecurity is from 2018 and is in the process of being updated.

With technology rapidly evolving, has the FDA consider updating guidance more frequently, and do you have the authority, the tools to update specific sections of the guidance that have to—maybe have to change more often to protect medical devices from cyberattacks? Would it be helpful for you to coordinate with CISA?

Dr. SHUREN. Well, I completely agree. This is an important topic. And it is not just about the security of medical devices. This really is about our National Security. We have seen a rise in cybersecurity risks and incidents over the past few years. We have had to put out 11 communications on this.

We have folks who are intending to either, they may not be intending to go for the medical device, they are in fact intending to get to the network system to which the medical device connects. We recently updated the guidance that you talked about. It was based upon feedback we got on the 2018 guidance, as well as additional lessons learned. So that is currently out for public comment.

We agree with you, we would like to continue to keep that fresh because it is constantly changing. Two things would be very helpful. One is, and we have this in the budget proposal for this year of 2023, funding for us because we only have gotten, and we are thankful for this $500,000 in our base to support medical device cybersecurity and that is it.

We have asked for $5 million. The other is authorities, because this is a place where we do not have the full authority to assure that these devices are cyber safe. And if we don't, we are going to continue to have threats. We have already seen the cost of ransomware, medical devices directly impacted and patient care directly impacted.

Senator ROSEN. Well, I might suggest that you speak with CISA. They have some shields up, a shields up program, other programs about good cyber hygiene for companies and might be a place that you can direct folks and as we work on getting——

Dr. SHUREN. But we actually are strong partners with CISA. We also work with the National Security Council, the National Cyber Chief. The little money I got, I was able to hire someone. She is working there part time, they took her——

Senator ROSEN. Wonderful.

Dr. SHUREN. We work with the FBI. We work with all those. In fact, they depend upon us for the information on medical devices, which is why it is so important we have the expertise and the authorities to be able to do our part of the job so they can do their part of the job.

Senator ROSEN. Wonderful. Thank you. I would like to move on and talk about UNLV, University of Nevada, Las Vegas, University of Nevada Reno. They both participate in network funded in the NIH to enhance translational research.

UNLV serves as a host institution to advance research in Alzheimer's, Parkinson's, and reducing health disparities. And UNR has done great work in a wide range of research areas, including cancer and diabetes. And we know the translational research, bridging the lab concept to impacting patients' lives, is an area that, of course, we must continue to strengthen. And so the research is happening at lots of universities, not just UNLV and UNR. It is critical to the pipeline of new treatments and cures.

Dr. Cavazzoni, does FDA currently provide outreach or learning opportunities for early career researchers to better understand the regulatory process, what could help advance their work to the next level, such as a spinoff company? And how can the FDA provide greater support to university research collaborations like these?

Dr. CAVAZZONI. Thank you for the question. We have—we do a lot of outreach and have partnerships with the academic community, and we view it as really an essential part of our job, particularly when it comes to translational research, because that is research that will allow us—will accelerate drug development in areas of unmet medical need by identifying new biological targets.

Also to help us understand potential surrogate markers of diseases that might allow us to use the great tools that Congress has given us, such as accelerated approval, expedited pathways to accelerate the delivery of drugs for—in areas such as neuroscience, Alzheimer's, Parkinson's, and so on. So we view it as a very important part of our job.

Senator ROSEN. Thank you.

I yield back, Madam Chair.

The CHAIR. Thank you.

Senator Baldwin.

Senator BALDWIN. Thank you, Madam Chair. I want to associate myself with Senator Cassidy's earlier comments relating to the Catalyst decision. And I know that I share a concern with many Members of the Committee about the ways in which drug companies can exploit loopholes in our existing laws, and I think Catalyst opens up another opportunity.

We are obviously looking at reauthorization and would love to see our legislation, that I am developing with Dr. Cassidy as an

amendment in that forthcoming package. I wonder if, Dr. Cavazzoni, if you could expand upon the potential impacts of this decision in the Catalyst case on patients and what the general concerns are at FDA about addressing drug development for rare diseases.

Dr. CAVAZZONI. Thank you, Senator. We share the concern and want to work with Congress to find a solution. The Catalyst decision will send a chill through the development of rare diseases, and it will disproportionately affect children with rare diseases. It is essential that we continue to generate and spur the study of drugs in children. And so this decision will really go counter to that.

I said, the situation right now is that, and as you heard from Dr. Marks, the situation following that decision is that a sponsor could study a disease in a very narrow segment of the population and then be able to block further approvals and throughout the entire, the entire condition that drug could address. So it is very concerning, and we appreciate Congress's interest and look forward to working with you.

Senator BALDWIN. Thank you. Dr. Shuren, I have long been concerned about our failure to protect consumers from harmful personal care products. As I noted during our last hearing, the FDA has extremely limited staff working to make sure that these products are safe despite the massive size of this industry. So, Dr. Shuren, yes or no, does the FDA have mandatory recall authority for personal care products?

Dr. SHUREN. That—although that isn't my particular area, I would be happy to take that back to the agency and get you an answer on that.

Senator BALDWIN. All right. Is anyone able to answer that question at this point, other witnesses?

Dr. SHUREN. My understanding is they don't, but I would like to confirm that for you.

Senator BALDWIN. Okay.

Dr. CAVAZZONI. I could try to chime in. So some of the over-the-counter products, such as, for instance, hand sanitizers are regulated as drugs. And the answer is no, we unfortunately do not have a mandatory recall authority for drugs, with the exception of biologics, where that authority has existed for decades. And that includes over-the-counter products that are regulated like drugs.

What happened with the adulterated or contaminated hand sanitizer last year exemplifies the challenges of not having that mandatory recall authority for drugs. We had a situation where hand sanitizers imported from one particular country were contaminated with methanol, which is a poison.

We had several deaths. We were able to intervene, but we could have intervened much faster and much more effectively had FDA had a mandatory recall authority for drugs, including over-the-counter drugs.

Senator BALDWIN. And if you are able, can you describe some of the instances in which the agency has requested companies voluntarily recall their products?

Dr. CAVAZZONI. We—that is a current process when it comes to drugs. We engage with the companies, and we ask them to withdraw voluntarily. Some companies, good actors, will do it very quickly.

However, some companies will take some time, and we have to engage in lengthy negotiations, often with—dealing with law firms who have been engaged on the company's behalf. And that takes time. And the clock is ticking when a poison is out there and it is either killing or making people blind, like the example that I gave you earlier.

Senator BALDWIN. Thank you.

The CHAIR. Senator Collins.

Senator COLLINS. Thank you, Madam Chair. It only seems appropriate, given Senator Baldwin's questions, that I thank you, Madam Chair, and Senator Burr, the Ranking Member, for working so closely with me and Senator Feinstein on our personal products bill, which we have had for two Congresses now. And this is an area where there is a gap in regulation, and I hope that we will be able to fill it. But I do want to thank both of you for—and your staffs for working so closely with us.

Dr. Cavazzoni, the Centers for Medicare and Medicaid Services recently finalized the national coverage determination for monoclonal antibodies directed at the amyloid plaque for the treatment of Alzheimer's disease. Under the NCD, if these monoclonal antibodies received accelerated approval, Medicare will cover them only in the FDA or NIH approved trials. Now, Congress charged the FDA, not CMS, to be the agency responsible for evaluating the safety and efficacy of biomedical products.

But CMS often makes coverage decisions on the basis of cost, an area where Congress has not empowered the FDA to weigh in. In this case, however, CMS routinely cites concerns about patient safety to justify their coverage determination, calling into question FDA's ability to evaluate this product class.

CMS is saying that in order to cover a drug that FDA has determined is safe for marketing, more safety data need to be generated. In light of the decision by CMS, do you question the FDA's decisionmaking regarding Aduhelm's accelerated approval?

Dr. CAVAZZONI. Thank you, Senator. First, I would like to emphasize how committed we are to continue to utilize expedited pathways, including accelerated approval, to bring medicines to underserved populations, such as people suffering from Alzheimer's. And our decision on aducanumab exemplifies our commitment, and we stand by that by decision. We believe that the data are solid, and that the drug is appropriately made available to patients based on FDA's decision.

It is important to distinguish FDA's role and CMS's role. So FDA is squarely and solely responsible for determining whether a drug is safe and effective. And we made that determination when we approved aducanumab. And that determination entailed our belief that—represented our belief that the drug can be made available to patients. Now, FDA does not have a role in making decisions about coverage.

CMS works in tandem with FDA and have a different standard than the safe and effective standard, which is reasonable and necessary. And based on that standard, CMS have made decisions about coverage and reimbursement, which translate into the setting in which they will be covering the drug for their beneficiaries.

Senator COLLINS. What concerns me in this case is not FDA's approach. I think you stayed within your lanes. Whether one agrees with the decision or not, you clearly state within your lane. But CMS did not because CMS commented not just on the reasonableness and the cost, but on the safety.

My next question for you is, do you think that CMS getting outside of its lane and imposing additional restrictions will affect the number of pipeline products that may be reviewed through this pathway and may be of benefit to those suffering from Alzheimer's?

Dr. CAVAZZONI. I cannot—I mean, I am not in a position to explain CMS's thinking. Having said so, when it comes to the pipeline, it is actually very robust. We have a lot of drugs in the pipeline for Alzheimer's disease, including drugs in the same class as aducanumab. It would be speculation to try to guess whether the decision might or might not impact future development.

Having said so, what I can tell you is that the pipeline is very healthy. And we are very encouraged by the advances that are taking place in the fields of Alzheimer's and neuroscience in general.

Senator COLLINS. I guess what I would respond to that is CMS is so broad in its coverage decision on this that I fear it will discourage research and have an impact on the pipeline of drugs. I hope I am wrong about that. My time has expired. Dr. Marks, I am just going to just submit for the record a question to you. I am receiving complaints that CBER is responding to meeting requests with a written response only, which is not nearly as valuable as sitting down and talking with drug sponsors. So I will submit that for the record, but I do think it is an issue.

The CHAIR. Thank you.

Senator Braun.

Senator BRAUN. Thank you, Madam Chair. Since I have been here in the Senate, I have been a disciple for fixing the whole health care system, along with the regulatory agencies that feed into it. It is a classic example of huge corporations, I think, involved with a very, very large and clumsy Government and a lot of it is needed. And Madam Chair refers to the gold standard of the FDA. Try explaining that to all of the rare disease victims out there and the families that have to contend with it.

I have a bill out there called the Promising Pathways Act, that simply says, acknowledge that it is a different dynamic when you have got maladies that have a prognosis of 2 to 4 years, 3 to 5 years, if you are lucky. You know, when we had the last hearing I felt that there is not enough attention being paid to that.

Do you think we have got the dynamism within the system that can differentiate between two different issues, those that have been around for a long while, where there is maybe plenty of options, even though the industry does things like patent tweaking and so forth—and I am doing this from the point of view of patients, em-

ployees, and business owners that don't own a health care company?

Let's, Dr. Marks, tell me what you think about, do you feel comfortable with the agility and the framework that is currently in place to address the issues that I am talking about?

Dr. MARKS. So thank you for that question. So we have tremendous flexibility that Congress has granted us with use of our accelerated approval program. That allows us to use a variety of surrogate and intermediate endpoints. It allows us to look at products that have been studied in as few as two handfuls of patients and potentially approve a product if they meet the standard for safety and effectiveness.

I think we have a tremendous essentially canvas to work with. Sometimes I think we have to be more creative with how we go about that. Toward that end, we are working in our Center toward trying to find ways to allow cell and gene therapies, particularly for very small populations. That is perhaps 10, 20, 30 people in the United States who might be treated with these to find their way into the marketplace more rapidly.

There are some work that has to be done there, and some of those actually may interface with some potential legislation that is pending that has to do with essentially using platform technologies. But we do have a tremendous amount of flexibility here. We have approved products on the basis of even eight patients worth of data when those data are very sound.

Senator BRAUN. Do you think we are using research and development from other countries that might be ahead of us—and again, I hear, well, that is done somewhere else? You know, we need to still run it through the gold standard of our own FDA.

We don't have the market cornered on all the best ideas. And if it is increasingly bureaucratic, and even though you say you have the ability to do this, should we be partnering up with other analogous agencies and efforts across the world?

Dr. MARKS. Thank you. We are very open to looking at data that come from trials conducted overseas. I do agree with you that to the extent, particularly for rare disease patients, we need to try to work with colleagues globally to benefit patients as much as we can. We will continue to do so. And that actually has been an area of focus of the Center working actually with WHO and partners in Europe.

Senator BRAUN. You know, in building a successful business over the years, you do two things well. You size up the market and you listen to the customers. And in this case, I was disappointed in the last hearing, we weren't getting patient input. You learn more there at the grassroots level than you many times do in the ivory tower.

I think it would behoove your entity to pay attention to the patients, the people out there talking about it, living with it. And many of these innovations, these new cures, aren't coming from big pharma because they don't get the return on investment.

You may want to look at doing something that gives extra help to the smaller companies and the startups that maybe wouldn't measure it in the same way. Do you think that has merit?

Dr. MARKS. Certainly it does potentially so. Very happy to continue to work with you on that.

Senator BRAUN. Thank you so much.

The CHAIR. Senator Marshall.

Senator MARSHALL. Thank you, Madam Chair. My first question for Dr. Cavazzoni. Last week we received a letter from Commissioner Califf on the FDA's changes to mifepristone risk evaluation mitigation strategies for medical termination of intrauterine pregnancies up to 70 days of gestation. I want to submit for the record a study from the Health Services Research and Managerial Epidemiology. And basically it talks about chemical abortion increased E.R. visits by 500 percent from 2002 through 2015.

As an OBGYN myself, certainly I was the doctor taking care of these complications, though I never would have ever considered prescribing this drug. Our big concern is this is now going to be done over the phone or through telemedicine. And based upon my clinical experiences, a woman's guessing of her gestational age is exactly that, it is a guess. And trying to make that determination, even physically by putting your hands on that woman's uterus, is off easily a month or two.

Really without an ultrasound, I am very concerned about this drug being prescribed through telemedicine or over the phone. How can the FDA stand by its current policy knowing there is a direct correlation between the E.R. visits and the chemical abortions, depending upon some other doctors to take care of the complications created by another physician or most likely a nurse practitioner PA's doing?

Do you think it is safe to mail these dangerous drugs, even potentially to underage women, without going through proper diagnostic protocols, including ultrasounds?

Dr. CAVAZZONI. Thank you, Senator. Just to clarify some of the aspects of this. As part of litigation that FDA was involved in, we undertook a review of the mifepristone, REMS, asking ourselves, is the REMS still necessary and should—and are any modifications warranted to the REMS based on the data that are available?

Under this exhaustive review of the data, which entailed data from our adverse event reporting system, data submitted from stakeholders, the litigants, and the sponsor, we concluded that the REMS has to stay in place. And the REMS entails a requirement for a confirmation of gestational age.

It is not prescriptive on how that is done. It leaves it up to standard of care for the prescriber, but it does require confirmation of—evaluation of gestational age. We also determined that as part of the REMS modification, the drug is safe and effective.

The benefit outweighs the risk if the in-person dispensing requirement is removed. Having said so, we also introduced a new requirement for pharmacies to be certified in order to be able to dispense the drug.

These are the safeguards that are in place right now. And we believe that those safeguards will ensure that the drug is—that the drug's benefit outweighs its risks.

Senator MARSHALL. Yes, I can only wish the people prescribing these drugs were in the E.R. taking care of these patients at midnight, and 2 in the morning, and taking care and seeing the complications from the drugs themselves. And my guess is this will turn into a huge technology financial gig for certain companies.

They will set this up to be very profitable. And many, many women are going to be harmed because of your decision. Dr. Marks, Senator Cassidy, Smith, and I championed the Ensuring Innovation Act, which prevents so-called evergreening, where brand name drug makers make not so innovative modifications to active ingredients and get additionally exclusivity.

I am now hearing their brand name drug makers are using slight modification in its inactive ingredients, as well as something as simple as changing the gauge, so that the next biosimilar isn't interchangeable. Does FDA have authority to recognize these loopholes and stop it?

Dr. MARKS. So we do have the ability to take care of some of this. I am going to pass this to Dr. Cavazzoni, who is—handles most of these products.

Dr. CAVAZZONI. So thank you for that question. Advancing the development of interchangeable biosimilars is a priority of the BsUFA program.

The BsUFA III commitment letter gives us additional tools that will allow us to put even more effort into this, including the issuance of a very foundational guidances to guide developers on how to develop interchangeable biosimilar, as well as a new regulatory science pilot program that is really geared toward identifying novel approaches in science to accelerate the development of interchangeable biosimilars.

We are aware that there is some interest in Congress to also look at clarifying the parameters or the situation around exclusivity for biosimilars, to clarify that two biosimilars that are approved, interchangeable biosimilars that are approved on the same day would be able to share exclusivity.

We support any new tools that would allow us to continue to advance their development.

Senator MARSHALL. Thank you, Madam Chair. I am over my time. I will submit for the record a question about using bioprinting to replace animal models. Thank you.

The CHAIR. Senator Hickenlooper.

Senator HICKENLOOPER. I am not sure this—is this on? Good enough. Thank you for your time and your service. This discussion, obviously, we have been in and out watching you on zoom and clearly the issues around how the FDA's approval, accelerated approval pathway has had great benefits for providing patients with serious life threatening diseases with timely access.

But it has come under increased scrutiny, and I know you have discussed Aduhelm a little bit earlier. Which it was approved against the recommendations of the Independent Advisory Com-

mittee, and the mismatch with the scientific recommendations could just as easily have gone the other way.

You could have, let's say the FDA did not approve a drug that otherwise got unanimous support from the Advisory Committee. So Dr. Cavazzoni, why don't we turn to you and say, how can we enhance agency processes to promote—to promote at the very least transparency, if FDA's decisions diverge from that of the Independent Advisory Committee?

Dr. CAVAZZONI. Thank you, Senator. Before I address your question directly, I would like to clarify a couple of points. As we reviewed the data for aducanumab, we in fact took the input from the Advisory Committee into consideration, and we actually heard from the Advisory Committee that the data in the application did not support approving the drug use in the traditional approval pathway.

We continued to review the data over the months that followed the Advisory Committee, and also became aware of additional data from other drugs that are developed in the same class, we concluded that the data in the application supported approving the drug use in the accelerated approval pathway. And we are always very, very grateful for the input from our Advisory Committees, and we listen very carefully.

Now there are some areas, when it comes to accelerated approval, where we could use some help from Congress. We currently work with sponsors to make sure that they meet their commitments to conduct confirmatory trials, and they do so within the timeframe that we establish that approval.

Having said so, we don't have the authority to require that confirmatory trials be started or underway by the time the drug is approved, or if they are not started, that the sponsor provide a very detailed plan to conduct those trials in a way that is feasible and that will meet the timelines and the milestones that we have established.

Another area where we could use some help in is in expediting the withdrawal of drugs when the confirmatory trials do not confirm that the drug is associated with clinical benefit. And right now the expedited withdrawal path is anything but expedited. It will take up to years. It will require lots of resources and lots of administrative burden.

We could use help in shoring up advisory—the very important accelerated approval tool that you have given us to—in those two areas.

Senator HICKENLOOPER. Yes, I can imagine that would be very difficult, but I appreciate that. I was asking more about transparency. When you do have a different result than what the Advisory Committee says, right now it is not clearly stated why that—why you diverged. You gave an explanation now, but that was not what came out then.

Dr. CAVAZZONI. And thank you for clarifying and my apologies for not addressing that point. And we have a lot of information in our reviews. And the—if one looks at the review of aducanumab, for instance, there are hundreds and hundreds of pages that will

lay our rationale, our thinking about the data and our rationale for approving the drug using accelerated approval.

Certainly we welcome additional ways in which we can have more transparency in the space. For instance, we already have a website that lists all of the surrogate endpoints that are being used for accelerated approval and traditional approval.

Senator HICKENLOOPER. Great. Thank you. Dr. Marks, I was going to ask you about the—how we can leverage the window of opportunity we have from this pandemic before what we know will be the next pandemic, to see if we can be better prepared.

Asking how we can help accelerate and encourage biomedical research on pathogens of pandemic level concern, so we are prepared for future threats. Maybe you can give a 30 second answer now, if that is okay with the Chair, and then I will submit this in writing, and we can have a more thorough answer.

Dr. MARKS. So in 30 seconds, I think we have to leverage what we did best during this pandemic, which was to have very good active dialog with those in the development stages of this. And to strengthen our manufacturing-type capabilities, so that when we do have a new pathogen and we do develop something, we are able to manufacture it very rapidly.

Senator HICKENLOOPER. Great. Well, so concise.

I yield back to the Chair.

The CHAIR. Thank you.

Senator Burr.

Senator BURR. Thank you, Madam Chair. I have one question and a few comments. Peter, I can't—excuse me, Dr. Shuren, I can't let you get out, Jeff, without talking about TAP. You and I sort of look at the same room from two different windows. As you know, I am not too excited about it. But let me ask the question in this way, what performance goals do you want us to put in the statute?

Dr. SHUREN. I think what is in the commitment letter is the right place to start. And we will learn from the pilot what is the best way to make this work optimally. And from there, we will also be well informed about what additional metrics go in. I will tell you, quite frankly, I would like to see us shorten the time from when you go from concept—it is really the development phase, that valley of death.

You said before, we get so focused on pre-market review, but the most important time is everything that leads up to that moment, because if you do that right, pre-market review should be a coronation. And TAP is about addressing the development side of the house. I would love to shrink that.

Today, it is hard to get the data to really know what real time is involved there and how to compare apples to apples for different kinds of technology. But that is what I would love to see down the road. We are not ready for today.

Senator BURR. When you leave, I hope you will think about this a little bit because I have given you the opportunity to tell us what tools we should use to measure the success of the pilot program. I want to stress, of the pilot program. Right now, I am not sure

that there are metrics or guardrails or goals that give us something to measure.

I don't want you to fall into a situation where 3 years from now you are coming back and say, we have got to permanently put this in, and you have got Members who are going, how do we know, or do we just take your word for it that it has been successful? I mean, we have got accelerated pathways out there, as you know. I think the authority—the opportunities already exist for everything you are trying to design in TAP. So I think you can do them today. But think about it.

Tell us what you would like to have in statute versus leave it up to me, because there will be something in there that I think will allow Members to get you in the future. I would rather you be the author of it. Peter, just want to comment on one thing you said, global collaboration. I agree with you. It is robust. It is getting better. But I want to remind you that global collaboration and acceptance of foreign data are two different things. And the authorities existed at FDA since 1997 when I did the predominant bill. But we really didn't accept foreign data until COVID.

My hope is that is one of those reflection points that we will look going forward at how we use more foreign data in substantiation of the applications versus to roll this back. I think you guys deserve a tremendous amount of credit going through two and a half years of hell.

Every Center, and the overall FDA, and how you have handled it, how you have taken advantage of the authorities that we presented that none of us ever knew whether we would ever need, but we needed every one of them that were out there, and the Chair and I are trying to comb through to figure out how we can envision—how visionary we can be in redesigning this for things that might be needed in the future for all of you.

I just can't thank you enough for the performance of the individuals that work in each of your centers, because I know they have put in long hours over a protracted period of time, and unfortunately I don't see yet an endpoint to this.

I see light at the tunnel, I just don't know whether it is a train or the sun. But just to understand, we are in this with you together. And Dr. Cavazzoni, I just want to commend you. You have been criticized greatly for using—for making a decision to approve using endpoints, surrogate endpoints for Aduhelm.

I think it is the right thing to do. I think the point that Senator Collins was trying to make is that when we have innovation like that, in an area that everybody is out trying to find something that helps Alzheimer's patients and other disease categories that are out there, and we do an approval at FDA, and CMC then limits the people who it would be applicable to—even as severely as what they just did. They have just crushed the capital markets that financed the development of that drug.

This is sort of my last opportunity to say to you guys. What—the capital markets, how they look at what you do and the products that come out, is absolutely crucial to our success in this Country. If in fact, they are not shareholders that are going to invest in

these companies, if there is not private capital that is chasing that two person innovation bench, Peter trying to get that next technology out, whether it is mRNA or something else, if they don't see when you approve those technologies that you don't have to go back through approval when it is used for a new indication, just the clinical trials for the new indication, those are the messages we send out there to fuel more of this innovation and growth in the market.

We have had a great success, I believe, and we have got another agency of the Federal Government that just absolutely cut our legs out from under us. And I would tell you, it is going to be devastating if you look at biotechnology and you look at how much investment is going into the field right now, it is at one of the lowest points that we have seen since it has been tracked.

It is cut in half from where it was pre-pandemic. Don't know the reason. But I can assure you that if we want the capital to flow for these innovative new technologies that may have the key that unlocks the door to this cancer cure or HIV aids or something else, we have got to fuel those research ventures. It is not going to be discovered internally within Government.

It is going to be some promising person, just like we got—oh, that is the advantage to getting old, you forget words. But we had a breakthrough with one particular scientists, immune—I can't come up with it. But it is a whole new category of cancer treatment today. You know what I am talking about.

Had we not financed that from NIH, we wouldn't have that fourth or fifth, I can't remember, treatment pathway that we have got. All because of one guy. And we can't look out and say, here is the one. So we have got to place bets across the board, and they have got to have financing to be able to get, Jeff, to where you talked about, the valley of death, and then we have got to figure out how to get them through it.

Madam Chair, thank you. I look forward to going forward on the Committee's work. Once again, I thank all of you for the job that you do, and more importantly, the people that are behind you at the agency. Thanks.

The CHAIR. Thank you, Senator Burr. Dr. Cavazzoni, just for the record, FDA has confirmed the safety and effectiveness of mifepristone, which FDA approved, I believe, over 20 years ago. Is that correct?

Dr. CAVAZZONI. That is correct. And—my apologies. After our review of the REMS, and taking into consideration the modifications that we made, we conclude that the benefits outweigh the risk, and the drug is safe and effective.

The CHAIR. Thank you very much for clarifying that. Dr. Shuren, for years I have called on FDA to improve surveillance of medical devices to protect patients from infection and other dangers. Actually, 7 years ago, I asked my Committee staff to investigate a series of dangerous infections in my home State of Washington linked to contaminated medical devices. And we found at least 25 different outbreaks of antibiotic resistant infections connected to the device that sickened over 250 patients worldwide.

FDA has to have the tools and resources it needs to ensure the safety of medical devices. How does the user fee agreement help enhance FDA monitoring of medical devices that are on the market?

Dr. SHUREN. Well, currently the scope in MDUFA does not include post market surveillance. It certainly was a topic that we had raised and discussed in negotiations. We did feel it was important to reach accord with industry, to have a consensus agreement. I know there were differences of opinion here that maybe it would be better to fund it through appropriations.

That said, I think the agreement we have is still a strong one and ultimately does help for patients in assuring timely access to safe and effective devices. I think it supports more of our work under the Safer Technologies Program, or at least it tackles the side of the equation about having safer devices on the market, but it does not currently cover once those devices are on the marketplace—continued monitoring and surveillance——

The CHAIR. So post-Market surveillance is not covered?

Dr. SHUREN. Is not currently covered.

The CHAIR. Thank you. Thank you for clarifying that. That will end our hearing today. And I want to thank all of our colleagues for their participation and our witnesses, Dr. Cavazzoni, Marks, and Shuren.

Thank you for joining us today and answering your questions. For any Senators who wish to ask additional questions, questions for the record will be due in ten business days, May 10th at 5 p.m..

The Subcommittee on Employment and Workplace Safety will meet next week on May 3d at 10 a.m. in Dirksen 430 for a hearing on connecting workers and communities, preparing and supporting the broadband workforce. With that, the Committee stands adjourned.

ADDITIONAL MATERIAL

JOINT PREPARED STATEMENT OF PATRIZIA CAVAZZONI, PETER MARKS, AND JEFFREY SHUREN

Chair Murray, Ranking Member Burr, and Members of the Committee, thank you for the opportunity to testify today on the reauthorizations of the Prescription Drug User Fee Act (PDUFA), Generic Drug User Fee Amendments (GDUFA), and the Biosimilar User Fee Act (BsUFA), Medical Device User Fee Amendments (MDUFA) and the Food and Drug Administration's (FDA, the Agency, we or our) efforts to deliver timely access to safe and effective medications and medical devices for all Americans. We appreciate the efforts of Congress and this Committee in particular in successfully reauthorizing these programs in previous cycles, and look forward to continuing our partnership this year.

PDUFA

The PDUFA VII reauthorization proposal described below was submitted to Congress on January 12, 2022. The Administration looks forward to working with Congress on reauthorization of

PDUFA to continue to speed the development and approval of vital drugs and biologics that are safe and effective.

The timely review of the safety and effectiveness of new drug applications (NDAs) and biologics license applications (BLAs) is central to FDA's mission to protect and promote the public health—and PDUFA is essential to these efforts.

FDA is committed to scientific quality and integrity during its review process for marketing applications to ensure that the medications we approve are safe and effective for American patients. Before PDUFA's enactment in 1992, the Agency lacked sufficient staff to perform timely reviews or develop procedures and standards to ensure a consistent and predictable premarket review process. As a result, Americans' access to innovative, new medicines often lagged behind other countries.

The enactment of PDUFA I in 1992, and subsequent reauthorizations, have addressed these challenges. Specifically, PDUFA authorizes FDA to collect industry user fees to, among other things, hire additional staff, and manage and enhance information technology systems. The user fees collected under PDUFA have enabled the Agency to speed the application review process for new drugs and biological products without compromising FDA's high standards for new drug safety, efficacy, and quality.

Speeding Americans' Access to Safe and Effective New Therapies

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

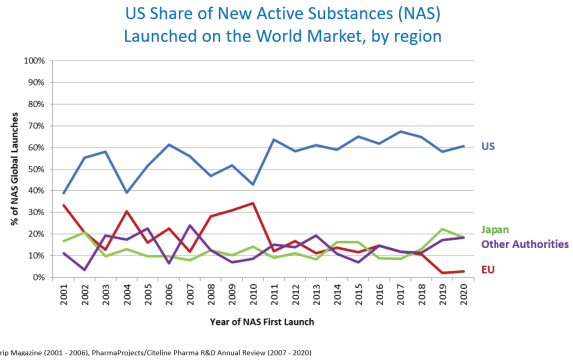
The PDUFA program began with a general focus on shortening review times, and its scope has expanded beyond the time for review of an application. The 5-year reauthorization cycles for PDUFA support continuous program innovation, evaluation, and improvement. The enhancements to the process for the review of human drug applications originally focused on the FDA pre-market review of NDAs and BLAs. Through successive PDUFA reauthorizations, program enhancements have evolved and expanded to include extensive communication and consultation between drug sponsors and FDA throughout the drug development process. These enhanced interactions give us the opportunity to provide more guidance to sponsors, including setting clearer expectations of what data are necessary to properly review and evaluate a drug, improving the potential for first-cycle approval, and getting safe and effective drugs to patients sooner—supporting FDA's mission. These interactions also enable sponsors to incorporate advances in regulatory science into their development programs, expediting drug development and facilitating timely regulatory decisions.

As discussed in more detail below, PDUFA VI included additional resources for breakthrough therapy review to expedite those products that offer early promise of benefit over existing therapies, initiated pilot programs for complex innovative trial designs and model-informed drug development, and expanded the provisions of the 21st Century Cures Act (CURES) in its focus on activities for patient-focused drug development and use of real-world evidence

(RWE) in regulatory decisionmaking. The continued modernization of drug review under PDUFA is supported by FDA's enhancements in informatics and hiring practices, including the Agency's implementation of hiring authorities under CURES to bring top talent to the Agency enabling us to consistently meet or exceed PDUFA commitments.

With these enhancements the United States continues to be a global leader in drug innovation and Americans are now typically the first to benefit from new safe and effective medicines. As shown in the figure below, this is a consistent pattern for novel drugs and biological products and while it may also be influenced by other factors, e.g. economics, it would not be possible without a robust approval process that is predictable and efficient. As shown in Figure 1, today, almost two-thirds of new active substances approved in the world market are launched first in the United States.

Figure 1: U.S. Share of New Active Substance Launched on the World Market, by region

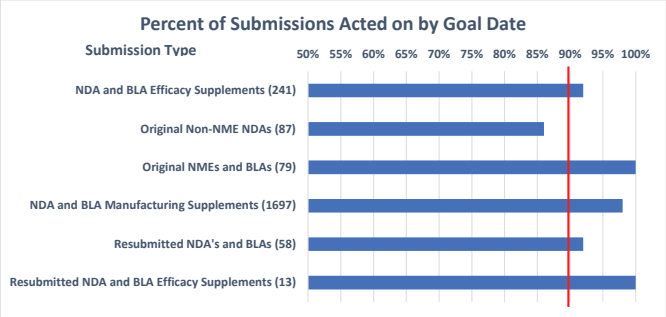


**New active substances (NASs): new chemical or biological entities where the active ingredient had received no prior approval for human use.*

Throughout this program evolution, FDA has continued to review large volumes of submissions and to deliver predictably high levels of performance against PDUFA goal commitments for timely regulatory review, as shown in Figure 2, below. This was accomplished even as FDA witnessed an unprecedented increase in submissions during the COVID–19 pandemic, and as FDA facilitated the development of therapeutics and vaccines, resulting in the authorization and approval of numerous COVID–19 vaccines and treatments.

**Goal 90 percent*

Figure 2: FDA Review Performance—FY 2021: Percent of Submissions Acted on by Goal Date [1]

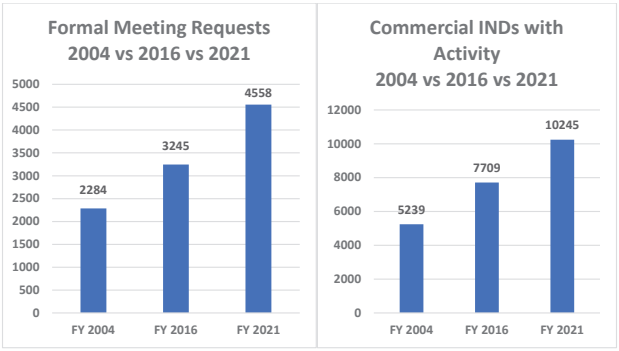


**Goal 90%*

Increasing the Timeliness and Efficiency of Premarket Review

A key element of the success of the PDUFA program is the ongoing development-phase consultation FDA provides to drug sponsors. FDA's capacity to provide sponsors, including small first-time innovators, with timely advice enabled by PDUFA funding, has contributed to the strong drug development pipeline in the United States today. This is reflected in the increased numbers of drug development programs underway (measured by commercial INDs with activity), and the corresponding growth in company requests for development-phase meetings, as shown in Figure 3.

Figure 3: fiscal year 2004, 2016, and 2021 Formal Meeting Requests and FDA Commercial Investigational New Drug (INDs) with Activity



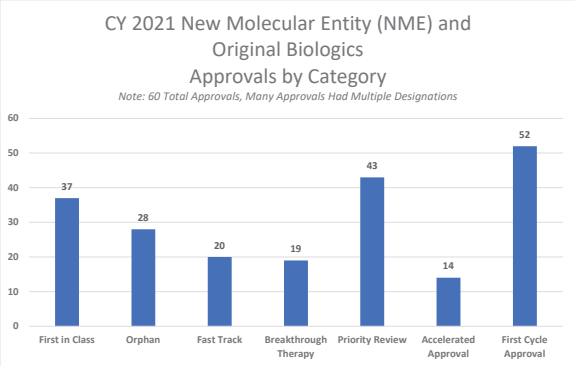
The volume of formal meetings requested by drug sponsors has steadily grown over the course of PDUFA. Early and frequent communication between sponsors and FDA serves to improve the efficiency of drug development. These meetings help sponsors navigate key milestones during drug development, increase the likelihood of well-designed and executed studies, and enable sponsors to clarify

[1] NME = New Molecular Entity; NDA = New Drug Application; BLA—Biologic Licensing Application

well-designed and executed studies, and enable sponsors to clarify requirements for complete application submissions and potentially avoid the need for an additional review cycle, translating into earlier treatments and cures for patients.

The improvement in the quality of drug development programs and the submitted applications, supported by these PDUFA-enabled consultations, is an important factor that explains the 87 percent first cycle approvals (52 of 60) of applications for new molecular entity (NME) NDAs and BLAs. Figure 4 provides key attributes of NME approvals for the calendar year 2021.

Figure 4: CY 2021 New Molecular Entity (NME) and Original Biologics Approvals by Category



Development-phase consultations can be particularly helpful in support of the most innovative or challenging drug development programs. For instance, of the NME, NDAs, and BLAs that FDA approved in calendar year 2021, close to half (47 percent) were indicated for rare diseases. In addition, over half (61 percent) of the drugs and biologics approved were first in their class, i.e., drugs and biologics with different mechanism of action from existing therapies.

While the standard review target for NMEs and original biologics submissions that are filed is 10 months after the 60-day filing date,[2] FDA expedites review for eligible drugs through a priority review, with a goal to review drugs within 6 months after filing. Priority review is generally targeted at drugs for serious conditions that, if approved, would provide significant improvements in safety or effectiveness in safety or effectiveness in safety or effectiveness.[3] In 2021, 43 of 60 NMEs and original biologics (72%) were designated for priority review.

Many drugs and biological products that receive priority review also benefit from other expedited programs intended to accelerate development, such as fast track designation and breakthrough des-

[2] There is a 60-day filing review period, which begins on the date FDA receives the application, to ensure the application is substantially complete and meets filing requirements. For non-NMEs the standard review target is 10 months after receipt date not the 60-day filing date.

[3] Priority review is also available for a drug designated as a qualified infectious disease product, certain supplements that propose a labeling change pursuant to a report on a pediatric study, or an application or supplement submitted with a priority review voucher.

ignation. Both these programs offer greater interactions between sponsors and FDA reviewers throughout the development process, including FDA providing advice on the design and implementation of the clinical trials necessary to demonstrate product safety and effectiveness. In addition, breakthrough designation typically includes greater involvement of FDA leadership. For cell and gene therapies, the Regenerative Medicines Advanced Therapy (RMAT) designation program is designed to expedite the review of cellular and gene therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies for which preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. RMAT designated products receive the same benefits as breakthrough therapies and approval of cell and gene therapies that have RMAT designation may be able to fulfill post-approval requirements by other than traditional clinical studies.

Accelerated approval, another expedited program, also speeds the development process by shortening premarket clinical trials using a surrogate endpoint reasonably likely to predict clinical benefit with a requirement to confirm clinical benefit in the post market setting. Thirty-nine of the 60 NME approvals of 2021 (65 percent) used one or more expedited programs, specifically fast track designation, breakthrough designation and/or accelerated approval.

COVID–19

As part of the government wide response to the COVID–19 pandemic, the Agency has been working around the clock over the past 2 years to facilitate the development and availability of therapeutics and vaccines as expeditiously as possible. FDA accelerated the development and publication of guidance and other information for industry and researchers on developing COVID–19-related treatments and vaccines.

In March 2020, FDA announced the creation of an emergency review and development program for possible therapies for COVID–19, the Coronavirus Treatment Acceleration Program, or "CTAP." The primary goal of CTAP is to help accelerate the development of therapeutics for patients and consumers. The Agency supported the program by reassigning staff and working continuously to review requests from companies and researchers who are working to develop therapies. Under CTAP, FDA is using every available authority and appropriate regulatory flexibility to facilitate the development of safe and effective products to treat patients with COVID–19. As of February 28, 2022, there were more than 690 drug development programs in the planning stages and we reviewed more than 470 trials of potential therapies for COVID–19. These include antivirals, immunomodulators, neutralizing antibodies, cellular and gene therapies, and combinations of these products. The diversity of therapeutic approaches being investigated is important because it rapidly expands our understanding of the effect of different categories of potential treatments. In addition, drugs have been identified that meet the standard for emergency use authorization, and FDA has acted to make these products available while continuing to collect information about their safety and effectiveness. As of April 18, 2022, the Agency authorized 15 drugs and non-vaccine bi-

ological products and approved one antiviral drug. Notably, these drugs are authorized or approved for the continuum of medical needs, from pre-and post-exposure prophylaxis, to treatment of outpatients with mild-moderate disease, to treatment of hospitalized patients with severe or critical COVID–19.

As of April 18, 2022, FDA has authorized three COVID–19 vaccines. All three vaccines are authorized for individuals 18 years of age and above with one of these vaccines authorized for individuals as young as 5 years of age. FDA has also approved two COVID–19 vaccines, one of these vaccines is approved for individuals 16 years of age and above and the other is approved for individuals 18 years of age and above.

In addition to providing access through authorizations and approvals, since the start of the pandemic, as of February 3, 2022 CDER has authorized over 2,100 expanded access requests for COVID–19 therapeutics, including emergency requests and CBER authorized 6,306 expanded access requests, 6,084 (96 percent) of which were in support of COVID–19 convalescent plasma.

Over the past 2 years, FDA has continued to work at a pace that is unprecedented, and not sustainable outside of an emergency, to deliver authorized and approved therapeutics and vaccines with unparalleled speed to the meet critical public health needs. Notwithstanding the increased workload, the average time between the request and meeting with sponsors for COVID–19 products was reduced by 50 percent. Although not all COVID–19 work is supported by user fees, without the staff, expertise and infrastructure provided by PDUFA user fees, our COVID–19 efforts would have been impossible to carry out. Furthermore, it is a testament to the seriousness with which we take our commitments under PDUFA that we continued to succeed in meeting key PDUFA commitments in the face of a large increase in non-PDUFA COVID–19 work. For instance, in fiscal year 2020 FDA received 46 percent more new INDs and 26 percent more formal meeting requests compared to fiscal year 2019.

PDUFA VI—Fulfilling Our Commitments

We are currently in the final year of the PDUFA VI program. Since the enactment of PDUFA I in 1992, the complexity of scientific and clinical issues in the study of new drugs has grown, including the use of genetic targeting, biomarkers, novel trial designs, and plans and programs to ensure effective post-market risk management relying on the Sentinel system, one of the largest RWE sources in the United States. In addition, PDUFA has enabled FDA to provide increased communication and consistent guidance during drug development and application review, a top priority for drug sponsors.

PDUFA VI (FY 2018 to fiscal year 2022) built upon the achievements of PDUFA V and committed the Agency to numerous initiatives to ensure the continued success of the human drug review program including:

- Capturing the patient voice in drug development;
- Ensuring sustained success for breakthrough therapies;
- Enhancing biomarker development;

- Advancing the use of complex innovative trial designs and model-informed drug development;
- Streamlining the review of combination products;
- Enhancing the use of RWE;
- Hiring and retaining highly qualified staff; and
- Enhancing the management and transparency of user fee resources.

The Agency's progress on these priorities is detailed below.

Capturing the Patient Voice in Drug Development

Elevating patient voices in developing new drugs to treat their diseases and conditions was a central part of PDUFA VI. The commitments in PDUFA VI complemented the patient focused-drug development (PFDD) provisions in the CURES Act by leveraging essential patient input and insights to fight disease.

Under the PDUFA VI authorization, the Agency focused on a series of four methodological PFDD guidance documents to address, in a stepwise manner, how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers. This series of guidance documents is intended to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful patient and caregiver input that can better inform medical product development and regulatory decisionmaking.

In addition, over the course of PDUFA VI, FDA engaged with patient advocacy groups to support their conduct of 54 externally led PFDD meetings and convened five public workshops to allow the patient voice to inform not only the above guidances but other disease specific development programs.

Ensuring Sustained Success for Breakthrough Therapies

The Breakthrough Therapy designation program is designed to expedite the review of therapies for serious conditions that show preliminary clinical evidence of a substantial improvement on a clinically significant endpoint over available therapy. This program has become a critical component of the human drug review program with requests and designations far exceeding expectations. PDUFA VI sought to ensure the sustained success of the breakthrough program by investing additional resources into the program. For the first 4 years of PDUFA VI, fiscal year 2018—fiscal year 2021, FDA received 586 breakthrough requests and granted 248. Drugs approved during PDUFA VI with breakthrough therapy designation include many new options for both adult and pediatric patients with cancer. Targeted oncological therapies with breakthrough designation included treatment for metastatic cancers with NTRK fusion proteins and a host of new treatments for non-small cell lung cancer targeting clinically relevant biomarkers—ALK, EGFR, MET, RET and KRAS. In addition, novel treatments with breakthrough designation were approved across many other cancers including breast cancer, bladder cancer, lymphoma, cholangiocarcinoma and rare tumors such as tenosynovial giant cell tumor and plexiform neurofibromas. Rare disease approvals during this period included the first triple therapy for the most common

cystic fibrosis mutation, the first therapy to treat heart disease (cardiomyopathy) caused by transthyretin mediated amyloidosis, treatment for Hutchinson-Gilford progeria syndrome, and the first therapy for thyroid eye disease.

Enhancing Biomarker Development

FDA and industry share the goals of the CURES Act and PDUFA VI to accelerate development of reliable biomarkers to advance important new therapies. Biomarkers are currently used throughout the drug development process, including as surrogate endpoints to support earlier evidence of effectiveness for regulatory decisionmaking when evidence from a clinical endpoint could take much longer or require many more patients to be studied.

A surrogate endpoint that is well established to predict clinical benefit, such as blood pressure as a predictor of risk of stroke, or viral load in certain infectious diseases, is considered validated and can be used to support traditional approval. Other surrogate endpoints are those for which there is evidence that they are reasonably likely to predict an improvement in a clinical outcome. Such surrogate endpoints may be used to approve a drug under accelerated approval for a serious or life-threatening disease for which there are not adequate therapies. For accelerated approvals, FDA requires post-marketing studies to verify the expected clinical benefit. FDA publishes a list of surrogate endpoints that have been used to support drug approval or licensure that includes whether the surrogate endpoint was used to support traditional or accelerated approval whether the surrogate endpoint was used to support traditional or accelerated approval whether the surrogate endpoint was used to support traditional or accelerated approval. [4]

Meaningful progress in developing additional biomarkers for public qualification requires a sustained effort and collaboration among a wide range of stakeholders. The Agency continues to have success via the Biomarker Qualification Program. In 2018, FDA qualified two additional biomarkers, one a safety biomarker panel to aid in the detection of kidney injury in early trials and the second a biomarker to monitor malaria treatment. Other promising biomarkers have progressed to the Qualification Plan stage, including biomarkers for important diseases such as inflammatory bowel disease, Parkinson's disease, emphysema, non-alcoholic steatohepatitis, osteoporosis and others. FDA continues to work with the National Institutes of Health, the Biomarkers Consortium, the Critical Path Institute and others to advance biomarker development under PDUFA VI.

Streamlining the Review of Combination Products

More streamlined review of combination products is another FDA and industry priority reflected in PDUFA VI. Combination products are therapeutic and diagnostic products that contain two or more types of medical products as constituent parts: a drug and device, a drug and biologic, a biologic and device, or all three (drug, biologic, and device).

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[4] *https://www.fda.gov/drugs/development—resources/table—surrogate—endpoints—were—basis—drug—approval—or—licensure*

Under PDUFA VI, FDA assessed combination product review practices. Based on the resulting recommendations, FDA pursued improvements in inter-center and intra-center combination product review coordination, consistency, and transparency for PDUFA products that are combination products regulated by CDER and CBER (PDUFA combination products), including through IT enhancements and training. FDA published several guidances regarding combination products to review more efficiently, effectively, and consistently combination products, including guidance that describes the ways in which combination product sponsors can obtain feedback from FDA on scientific and regulatory questions as well as best practices for FDA and sponsors when interacting on these topics. [5]

Advancing the Use of Complex Innovative Trial Designs and Model-Informed Drug Development

FDA routinely works closely with industry to facilitate innovative approaches to drug development that maintain our high standards for drug safety and efficacy. PDUFA VI encouraged these efforts by advancing Model-Informed Drug Development (MIDD) and the use of Complex Innovative Trial Designs (CID).

To fulfill the goals and commitments of PDUFA VI, the Agency developed the MIDD Pilot Program [6] and the CID Pilot Meeting Program. [7]

The MIDD Pilot Program is designed to:

- Provide an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development; and
- Provide advice about how particular MIDD approaches can be used in a specific drug development program.

Under the pilot program, FDA accepts two to four paired-meeting requests for meetings each quarter. For each meeting request granted as part of the pilot, FDA conducts an initial and follow-up meeting on the same drug development issues to occur within a span of approximately 120 days. Under the pilot program from fiscal year 2018—fiscal year 2021, FDA received 46 meeting requests and granted 38 of those requests. The total number of sponsor meetings during that time period was 43. The meeting requests spanned 14 different therapeutic areas—cardiology, oncology, non-malignant hematology, neurology, infectious disease, immunology/inflammation, dermatology, pulmonary, psychiatry, gastroenterology, ophthalmology, endocrinology, nephrology, and hepatology.

The CID Pilot Meeting Program developed under PDUFA VI is designed to:

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[5] *https://www.fda.gov/combination-products/guidance-regulatory-information/combination-products-guidance-documents*

[6] *https://www.fda.gov/drugs/development—resources—model—informed—drug—development—pilot—program*

[7] *https://www.fda.gov/drugs/development—resources—complex—innovative—trial—design—pilot—meeting—program*

- Facilitate the use of complex adaptive, Bayesian, and other novel designs in late-stage drug development; and
- Promote innovation by allowing FDA to publicly discuss the trial designs considered through the pilot meeting program, including trial designs for medical products that have not yet been approved by FDA.

Under the pilot meeting program, FDA accepts up to two meeting requests per quarter yearly. For each meeting request granted as part of the pilot, FDA conducts two meetings on the proposed CID within a span of approximately 120 days. From fiscal year 2018—fiscal year 2021, the CID pilot program received 15 meeting requests—13 for CDER and 2 for CBER—and granted five of the CDER meeting requests. The total number of sponsor CID meetings was 16, as FDA granted additional meetings during the 120-day span. The meeting requests spanned seven different therapeutic areas—neurology, oncology, malignant hematology, non-malignant hematology, pain, rheumatology, and gastroenterology.

Enhancing the Use of Real-World Evidence (RWE)

Medical care and biomedical research are amid a major transformation with data from electronic health records, insurance claims data bases, patient registries, digital health technologies, and other new sources comprising an immense new set of information about health and healthcare. Sponsors and the research community are seeking to take advantage of the quantity of data generated in routine medical practice to help inform regulatory decisions about the safety and effectiveness of drugs. Importantly, these real-world data (RWD) sources provide data about patients outside of structured clinical trial visits and in the social context of their day-to-day lives. These sources of data are now becoming increasingly available to researchers, clinicians, and patients with the potential to improve medical care and public health.

FDA recognizes the potential value of utilizing RWD to generate RWE in evaluating not only the safety of medications but also their effectiveness. Under PDUFA VI, the Agency continues to fulfill our commitment to enhance the use of RWE. The Agency has conducted multiple demonstration projects, engaged with external stakeholders, and to date published four guidances on the use of RWE in regulatory decisionmaking. For example, FDA published draft guidance with recommendations on using data from electronic health records, medical claims, registries, and data standards for applicable submissions containing study data derived from RWD sources. In addition, another draft guidance describes regulatory considerations for the design and conduct of non-interventional (or observational) studies.

Hiring and Retaining Highly Qualified Experts

To efficiently conduct reviews of human drug applications and meet PDUFA commitments, FDA must be able to hire and retain sufficient numbers and types of technical and scientific experts. To strengthen this core capability during PDUFA VI, FDA established a modernized position management system, more efficient recruiting practices, a dedicated scientific recruiting function and metric

goals for human drug review staff hiring. We also conducted a comprehensive independent assessment of hiring and retention system performance. The Agency thanks the Committee for providing vital hiring authorities in the CURES Act, greatly improving FDA's ability to hire and retain scientific experts in more complex and specialized areas and meet our growing responsibilities.

The Agency continues to put every effort into meeting our hiring goals under PDUFA VI. FDA is committed to hiring 230 Full-Time Equivalents (FTEs) from fiscal year 2018 to fiscal year 2022 as agreed upon in the PDUFA VI commitment letter. FDA has successfully hired 212 FTEs of the 230 FTEs (92 percent) as of September 30, 2021.

Enhancing the Management of User Fee Resources

FDA is committed to enhancing management of PDUFA resources and ensuring PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. Under PDUFA VI, the Agency established a resource capacity planning function to improve its ability to analyze current resource needs and project future resource needs, modernized its time reporting approach (e.g., ?99 percent of CDER and CBER employees time report), conducted an evaluation of PDUFA program resource management, and published a 5-year PDUFA financial plan with annual updates. [8]

In 2020, FDA embarked on its own initiative—not a PDUFA commitment—to modernize the New Drugs Regulatory Program. [9] These changes are intended to improve efficiency and consistency of our work to free up resources so that our scientists have more time to focus on the increasing challenges of drug development, particularly for unmet medical needs, and on the multiple collaborations needed to make sure candidate drugs are developed and assessed properly, with appropriate input from external scientists, expert physicians, and patient communities. The initiative includes regulatory and review process changes, as well as organizational restructuring and strengthening the institutional support structures, including personnel and information technology (IT), that underpin the regulatory process.

PDUFA VII Reauthorization

As part of PDUFA VI, Congress directed the Agency to reach out to all stakeholders to solicit thoughts and insights on PDUFA reauthorization and changes to PDUFA performance goals. FDA followed the process, as described in statute, in developing the recommendations for reauthorization. This included holding two public meetings, conducting negotiations with the regulated industry, and having regular consultations with stakeholders, including patient and consumer advocates. To ensure transparency in this work, the Agency posted the meeting minutes for the various en-

[8] *https://www.fda.gov/about-fda/user-fee-reports/user-fee-five-year-financial-plans*

[9] *https://www.fda.gov/drugs/regulatory—science—research—and—education—reorganization—office—new—drugs—corresponding—changes—office—translational—sciences—and—office*

gagements, including: the two public meetings; over 100 negotiation sessions with industry, and six stakeholder discussions. [10]

PDUFA VII Overview

Based on the maturity and success of the PDUFA program, the recommendations for PDUFA VII focus on ensuring FDA has capacity to review new and innovative products, including cell and gene therapy products. To provide the capacity needed to successfully implement the commitments outlined below, while maintaining current performance, PDUFA VII recommends increasing fees to fund 352 new staff and to support critical investments in program infrastructure, such as data IT modernization. The new staff and investments are scheduled to phase in over the 5-years of PDUFA VII.

The commitments thematically fall into the following categories:

- Enhancing CBER's capacity to support development, review, and approval of cell and gene therapy products and new allergenic extract products;
- Improving pre-market review processes and procedures;
- Enhancing regulatory science to expedite drug development;
- Enhancing regulatory decision tools to support drug development and review;
- Continuing enhancement and modernization of the drug safety system;
- Enhancing product quality reviews, chemistry, manufacturing, and controls (CMC) approaches, and advancing the utilization of innovative manufacturing technologies;
- Continuing enhancements for management of user fee resources;
- Improving FDA's hiring and retention of key scientific and technical talent; and
- Enhancing IT and bioinformatics goals.

Enhancing CBER's capacity to support development, review, and approval of cell and gene therapy products and new allergenic extract products

FDA has experienced exponential growth in cellular and gene therapy submissions over the past 7 years with over 1,993 active, development programs. We have seen a sustained increase in development program activities, including an 85 percent increase in original IND receipts, a 139 percent increase in IND amendment receipts, and a 158 percent increase in formal meeting requests. In addition, the RMAT program has advanced the development of a wide variety of cellular and gene therapies with many including orphan designations and for pediatric populations. From program initiation in December 2016 through 2021, 68 of 180 requests have received RMAT designation with three RMAT designated products receiving approval in 2021—two allogenic cellular products, one for immune reconstitution in pediatric patients with congenital

[10] *https://www.fda.gov—industry—prescription—drug—user—fee—amendments—pdufa—vii—fiscal—years—2023—2027*

athymia, one for wound healing, and a CAR-T gene therapy for B-cell lymphoma.

Therefore, PDUFA VII proposes new enhancements to CBER's capacity to support development, review, and approval of cell and gene therapy products to accommodate the current and expected influx of work in the coming years. The proposal will support development of multiple guidances, numerous public meetings to examine new technologies and approaches, a patient-focused drug development meeting to better understand patient perspectives on gene therapy products, and public outreach to facilitate product development and approval. In addition, if the negotiated commitments are adopted, new allergenic extract products will be included in PDUFA VII, and the program will provide needed resources to facilitate the development and approval of new therapies, including those for food allergens, which constitute most new allergenic extract products under development.

Improving pre-market review processes and procedures

Communication during drug development continues to be critical to successful drug development. PDUFA VII proposes several enhancements to the current robust communication framework. PDUFA VII proposes exploring a new pilot program for certain efficacy supplements, i.e., when a sponsor is seeking a new indication for an already approved product that would support review earlier than would otherwise occur with the goal of expediting patient access to novel uses for existing therapies. The proposal also seeks to expand communication and feedback during the drug development process by creating two new formal meeting types and allowing for follow-up opportunities after meetings.

Finally, the commitment letter also includes new performance goals for pre-approval review of postmarketing requirements (PMRs), studies done after a drug is on the market to further explore efficacy and or safety to ensure timely availability of information on the safety and efficacy of therapies. In addition, it includes a new process for reviewing sponsor-initiated requests to release the applicant from the requirement to perform a PMR study.

Enhancing regulatory science and decision tools to expedite development

Model-Informed Drug Development (MIDD) and Complex Innovative Design (CID)

PDUFA VII proposes to further enhance regulatory science and to expedite drug development by continuing FDA's successful CID and MIDD programs. Specifically, the proposed CID program will continue to facilitate the advancement and use of complex adaptive, Bayesian, and other novel clinical trial designs. The MIDD program will also continue to further advance and integrate the development and application of exposure-based, biological, and statistical models in drug development and regulatory review.

Advancing Development of Drugs for Rare Diseases

In addition, building on the success of the rare disease programs in CDER and CBER, a new pilot program will be launched to advance rare disease drug development by providing a mechanism for

sponsor discussion with FDA to facilitate the endpoint development process—often a critical challenge in efficient trial design.

Advancing RWE for Use in Regulatory Decision-Making

FDA will also build on its current RWE program with a new pilot program that seeks to improve the quality and acceptability of RWE-based approaches in support of new labeling claims, including approval of new indications of approved medical products, or to satisfy post-approval study requirements.

Enhancing Use of Digital Health Technologies to Support Drug Development

Recognizing the growth of digital health technology (DHT) and that remote data acquisition from patients and clinical trial participants has the potential to measure a wide range of activities, behaviors, and functioning in real-life settings that can inform important clinical endpoints, PDUFA VII proposes to establish a framework to guide the use of DHT-derived data in regulatory decision-making. FDA will undertake workshops and demonstration projects to inform this work and will address standardized processes for data management and analysis of large data bases from digital health tools.

Furthering the Patient Voice in Drug Development

PDUFA VII proposes to continue to enhance decisions to support drug development and regulatory review by advancing the patient's voice in drug development and decisionmaking through PFDD, including training and public workshops, and issuing guidance on the use and submission of patient preference information.

Furthering the Review of Combination Products

As noted, under PDUFA VI, the Agency took steps to facilitate the review and approval of combination products. PDUFA VII would add to these activities by introducing new procedures and timelines for use-related risk analysis and human factor validation study protocols as part of the combination products review process.

Continuing enhancement and modernization of the drug safety system

PDUFA VII proposes to continue enhancement and modernization of FDA's robust drug safety system by modernizing and improving Risk Evaluation and Mitigation Strategy assessments, including updates to guidances, policies and procedures, and new review performance goals. The proposal will optimize the Sentinel Initiative capabilities by enhancing analytic functions to help inform labeling on the safety of product use in pregnancy, to detect safety signals in a timely manner, and to advance the understanding of how RWE can be used to study effectiveness.

Enhancing product quality reviews, chemistry, manufacturing, and controls (CMC) approaches, and advancing the utilization of innovative manufacturing technologies

PDUFA VII proposes new enhancements related to product quality reviews, chemistry, manufacturing, and controls (CMC) approaches, and advancing the utilization of innovative manufacturing technologies by enhancing communication to promote more efficient and effective review through more structured CMC information requests. Also included is a commitment to notify sponsors

in advance of facility inspections where FDA needs to see the product being manufactured. Under the proposal, the Agency will issue guidance on FDA's thinking on the use of alternative tools to assess manufacturing facilities included in pending applications (such as alternative tools utilized during the COVID–19 pandemic). The proposal will also initiate a new pilot program to facilitate and expedite CMC development for products with accelerated clinical development timelines. Last, PDUFA VII proposes to advance the utilization and implementation of innovative manufacturing technologies through a public workshop and a published strategy document.

Continuing enhancements for management of user fee resources

PDUFA VII proposes to continue to enhance management of user fee resources by advancing FDA's resource capacity planning function and adjustment methodology, including a third-party evaluation of the methodology by 2025. The proposal will continue financial transparency by FDA issuing a 5-year financial plan and annual updates and holding annual public meetings to discuss PDUFA finances.

Improving FDA's hiring and retention of key scientific and technical talent

PDUFA VII proposes to further improve FDA's hiring and retention of key scientific and technical talent. FDA commits to report on FDA's website progress on annual PDUFA VII hiring goals. FDA also commits to utilizing an independent contractor to conduct a targeted assessment of the hiring and retention of staff for the human drug review program and will post this assessment on FDA's website.

Enhancing IT and bioinformatics goals

PDUFA VII proposes to enhance IT and bioinformatics by enhancing transparency of IT activities and modernization plans through regular meetings, publishing a data and technology modernization strategy, and engaging with external stakeholders on initiatives around data convergence. The proposal will modernize the Electronic Submission Gateway, explore cloud and cloud-based technologies, and leverage modern technology to accelerate CBER's data and technology modernization. Additional staff and resources are added in PDUFA VII to support review and analysis of the increasing amounts of bioinformatics and computational data submitted during product development and review, including the management of submissions with extensive and continuous data from digital health technologies.

GDUFA

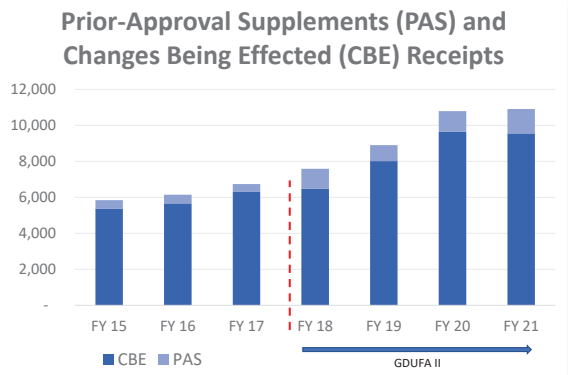
GDUFA has helped to significantly expand the timely availability of and patient access to affordable, high quality generic medicines since its inception. Patient confidence that generic drugs will work the same as brand products, and can be freely substituted, is the foundation for trillions of dollars in savings that generics have produced for the healthcare system.

The generic drug industry has grown from modest beginnings in 1984 into a major force in health care to reduce health care costs.

In the past 10 years (2011–2021) close to 1,000 first generic medicines have been approved, offering patients access to drugs for which there was no previous generic competition. FDA has also approved thousands of additional versions of generic medicines over this time, contributing to significant price reductions for consumers. According to the Association of Accessible Medicines, based on an analysis by IQVIA, generic drugs saved the U.S. health care system $2.4 trillion from 2011 to 2020.[11]

This success was enabled by the enactment of GDUFA I as part of the Food and Drug Administration Safety and Innovation Act of 2012 and reauthorization of the program (GDUFA II) as part of the FDA Reauthorization Act of 2017. While substantial progress has been made, there is still more to be done. With more generic drugs on the market there is a corresponding increase in the need for FDA regulatory activity over the lifecycle of these products. Indeed, we see a steady increase in approved abbreviated new drug applications (ANDA) with post-approvalactions, including Prior Approval Supplements and Changes Being Effected (CBE) submissions (Figure 5). Most of these submissions involve manufacturing facility and labeling updates. In addition, with the steady approval of new molecular entities and innovative new uses for previously approved drugs, including many new complex products, the GDUFA program faces increased industry requests for regulatory feedback to bring the next generation of generic drugs to the market.

Figure 5: Receipts of Prior-Approval Supplements and Changes Being Effected Submissions by Fiscal Year



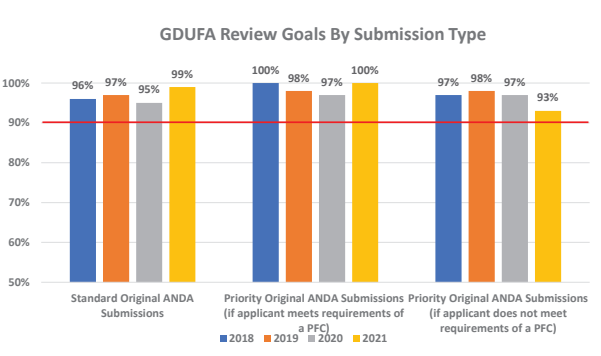
GDUFA II—Fulfilling Our Commitments

Under GDUFA II, FDA eliminated the backlog of hundreds of ANDAs and made significant progress in timely review of generic drug submissions. In the first 4 years of GDUFA II we approved over 3000 ANDAs and, to facilitate generic drug development, issued over 50,000 communications to industry. Under GDUFA II, the Agency committed to assess 90 percent of priority ANDAs with-

[11] Analysis done by IQVIA for 1255 generic molecules based on sales data and pre-patent expiry prices of brand name drugs *https://accessiblemeds.org—sites—default—files—2021—10—AAM—2021—US—Generic—Biosimilar—Medicines—Savings—Report—web.pdf*

in 8 months of submission and to assess 90 percent of standard ANDAs in 10 months. The program has surpassed its 90 percent goal for assessment of all original standard and priority ANDAs (Figure 6) and continued to meet or exceed the majority of its goals even during the COVID–19 pandemic, with over 1300 approvals for drug products used to treat patients suffering from COVID–19. For many of these COVID–19 approvals, the decision was made in less than half the applicable goal period. In addition, throughout GDUFA II, approximately 13 percent of annual ANDA approvals were for complex generics including the first generic inhaler for asthma and chronic obstructive pulmonary disease.

Figure 6: Achievement of GDUFA II Review Goals by Submission Type



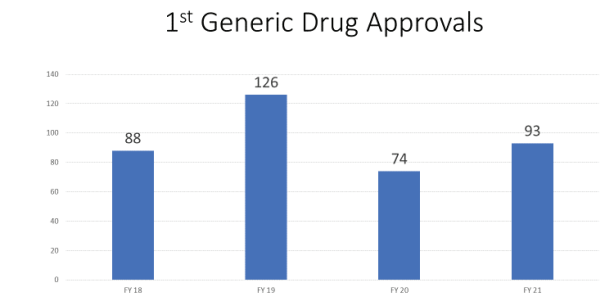
PFC—those applicants who met the requirements of the Pre-Facility Correspondence process (21 U.S. C. 355(j)(11)).

90 percent goal for all submission types

Faster assessment of priority ANDAs

Under amendments made by the FDA Reauthorization Act of 2017 (which authorized GDUFA II), priority review is available for applications for generic drugs with limited competition, as well as for generic drugs in shortage, that meet certain conditions. This includes the shorter review timeframe under the Pre-Facility Correspondence (PFC) framework, under which sponsors submit information about manufacturing facilities and testing of the drug not later than 60 days prior to the submission of the application. In addition, a core element of prioritization efforts under the GDUFA II commitment letter is to expedite the assessment of potential "first generic" ANDAs because they can open the market to generic competition for the first time. Many "first generic" ANDAs cannot lawfully be submitted until a specific date after the innovator drug was approved. Figure 7 shows the number of first generic drug approvals by fiscal year (FY) during GDUFA II.

Figure 7: First Generic Drug Approvals by Fiscal Year



To provide some clinical context for these numbers, Table 1 provides a summary of some significant first generic approvals for CY 2021. [12]

Table 1: Significant First Generic Drug Approvals in CY 2021

Generic Name	brand Name	Indication	Approval Date
Linaclotide Capsules	Linzess Capsules	Irritable bowel syndrome with constipation and chronic idiopathic constipation	Feb. 9, 2021
Apremilast Tablets	Otezla Tablets	Moderate to severe plaque psoriasis	Feb. 18, 2021
Ibrutinib Capsules	Imbruvica Capsules	Mantle cell lymphoma (MCL)	Mar. 31, 2021
Enzalutamide Capsules	Xtandi Capsules	Prostate cancer	May 14, 2021
Lenalidomide Capsules	Revlimid Capsules	Multiple myeloma, anemia, and certain lymphomas	May 21, 2021
Tofacitinib Tablets	Xeljanz Tablets	Certain types of arthritis and ulcerative colitis	Jun. 1, 2021
Difluprednate Opthalmic Emulsion	Durezol	Inflammation/pain associated with ocular surgery and treatment of endogenous anterior uveitis	Aug. 9, 2021
Varenicline Tablets	Chantix Tablets	Smoking cessation	Aug. 11, 2021
Linagliptin Tablets	Tradjenta Tablets	Type 2 Diabetes Mellitus	Aug. 31, 2021
Lenalidomide Capsules	Revlimid Capsules	Multiple myeloma	Oct. 14, 2021
Dasatinib Tablets	Sprycel Tablets	Chronic myeloid leukemia	Nov. 23, 2021

[12] Information on approval of first generics is posted on FDA's first generic drug approvals website https://*www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/first-generic-drug-approvals*

Pre-ANDA Program Enhancements

To reduce the number of cycles to approval, particularly for complex generic products, the GDUFA II commitment letter established a pre-ANDA program. This program helps clarify regulatory expectations for prospective applicants early in product development, assists applicants in the development of more complete submissions, and provides mechanisms for consultation regarding these products after the ANDA is submitted, thus promoting a more efficient and effective development and assessment process.

As detailed in the commitment letter, the GDUFA II pre-ANDA program established three types of meetings for complex products:

- Product development meetings in which FDA provides targeted advice concerning an ongoing ANDA development program.
- Pre-submission meetings, which give applicants an opportunity to discuss and explain the content and format of an ANDA before it is submitted.
- Mid-review-cycle meetings, which occur, as the name implies, around mid-cycle after the applicant has received FDA's assessment of any deficiencies in the application and provides the applicant an opportunity to discuss those concerns and plan for next steps.

During GDUFA II, the Agency has continued to grant these meetings and provided industry further information via the final guidance titled "Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry," released in November 2020. [13]

To facilitate development of new generic products, FDA issued Product Specific Guidances (PSGs) to assist the generic pharmaceutical industry with identifying the most appropriate methodology for generating the evidence needed to support ANDA approval, for both complex and non-complex drugs. Under the GDUFA II commitment letter, FDA established goals for issuing PSGs for non-complex new molecular entities. FDA has consistently met this goal and as of April 18, 2022, there were currently 1,978 PSGs available to industry. [14]

While the GDUFA II commitment letter did not include a goal around PSGs for complex generics, GDUFA supports a robust regulatory science program that supports the development of additional innovative methodologies and more efficient tools to help establish drug equivalence standards and support the development of, and access to, new generic drug products. FDA consults with and solicits input from the public, industry, and academic researchers to develop an annual list of the GDUFA regulatory science initiatives specific to research on generic drugs. In addition, we engage stakeholders through numerous scientific workshops and publish an annual report on accomplishments. [15]

Another tool in the pre-ANDA program is controlled correspondence, which allows potential applicants to submit targeted ques-

[13] *https://www.fda.gov/media/107626/download*
[14] *https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm*
[15] *https://www.fda.gov/drugs/generic—drugs—science—research*

tions regarding their drug development program and receive a response within a specific timeframe. Under the GDUFA II commitment letter, FDA made enhancements to its Inactive Ingredient Data base, which is an important tool for generic drug developers, to enable users to perform electronic queries to obtain Maximum Daily Intake and Maximum Daily Exposure information for each route of administration for which data are available.

ANDA Assessment Program Enhancements

Consistent with the statute, the GDUFA II commitment letter refined programmatic timeframes, including for sponsor communications, used in the ANDA assessment process. The ANDA assessment program starts with submission of an ANDA. When an ANDA is submitted, FDA first determines whether an ANDA is sufficiently complete to permit a substantive assessment. These "receipt" determinations are made within consistent timeframes. The Agency also increased receipt-related communications to facilitate the receipt decision and resolve certain receipt disputes within consistent timelines.

When a new ANDA is received and is under assessment, FDA communicates assessment deficiencies beginning at approximately the mid-point of the review. Communications continue on a rolling basis during the assessment. When deficiencies in an ANDA prevent FDA from approving it, FDA issues a Complete Response Letter (CRL) itemizing the deficiencies that must be corrected for the ANDA to be approved. The GDUFA II commitment letter established post-CRL teleconferences to allow applicants to seek clarification concerning deficiencies identified in CRLs. This helps applicants meet FDA's expectations when an ANDA is re-submitted for additional review. In 2021, FDA conducted 73 such teleconferences, 98 percent within 30 days of receipt of the written request.

Drug Master File (DMF) Assessment Program Enhancements

Type II DMFs are submissions from a third party other than the ANDA applicant that contain confidential information on a drug substance (or active pharmaceutical ingredient (API)) or drug substance intermediate (or materials used in their preparation) that the Agency evaluates independently. These submissions can be cross referenced by multiple applicants to support approval of their respective ANDAs. Effective communication between ANDA applicants, DMF holders, and FDA is essential to reduce the likelihood of potential problems that could delay approvals. The GDUFA II commitment letter featured new and enhanced mechanisms to facilitate this communication, including first adequate letters to indicate a DMF has no open issues related to the assessment of a referencing ANDA, no further comment letters, and expanded opportunities for DMF holders to request teleconferences with FDA regarding first cycle DMF deficiency letters.

Pursuant to the GDUFA II commitment letter, FDA issued a draft guidance [16] on post-approval changes to a Type II API DMF and submission mechanisms for ANDA applications which ref-

[16] *https://www.fda.gov/media/84217/download*

erence a Type II API DMF. FDA also issued a revised draft guidance titled "Completeness Assessments for Type II API DMFs under GDUFA." [17]

Facility Assessment Enhancements

To mitigate export-related challenges identified by U.S.-based API manufacturers, the GDUFA II commitment letter called for FDA to issue guidance and conduct outreach to foreign regulators on its risk-based manufacturing site selection model. To fulfill this commitment, we issued a manual of policy and procedures (MAPP) titled, "Understanding CDER's Risk-Based Site Selection Model" [18] in 2018, to explain how FDA determines which manufacturing facilities to prioritize for routine surveillance inspections. To mitigate ANDA sponsor concerns, FDA enhanced the speed and transparency of communications concerning facility inspection outcomes. Specifically, we implemented a process to notify facilities of final facility inspection classifications (i.e., No Action Indicated, Voluntary Action Indicated, or Official Action Indicated) within 90 days from the close of the inspection. In addition to enhanced transparency concerning the compliance status of GDUFA facilities and sites, FDA updates its publicly available facility inspection classification data base every 30 days to reflect the most recent surveillance inspection outcomes. [19]

Accountability and Reporting Enhancements

Under GDUFA II, enhanced information infrastructure and analytics increased transparency and accountability for meeting performance goals and strengthened program management and resource use. FDA developed internal processes to enable improved productivity and performance through regular assessment of progress toward GDUFA II goals. The Agency also enhanced the transparent and efficient administration, allocation, and reporting of user fee resources. We expanded GDUFA program reporting and provide the information on our website "Enhanced Accountability & Reporting." [20]20 Robust performance reporting enables Congress, industry, and other stakeholders to gauge the generic drug program's performance on an ongoing basis. FDA also issued a Five-Year Financial Plan in fiscal year 2018 with annual updates [21] and held an annual meeting [22] on financial transparency and efficiency of the user fee programs. In addition, an independent third party evaluated FDA's Capacity Planning Adjustment (CPA) methodology that in PDUFA and BsUFA adjusts target revenue annually as needed within a user fee cycle to account for forecasted, sustained increases in workload. This report specifically evaluated whether a proposed CPA methodology could be applied to the GDUFA pro-

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[17] *https://www.fda.gov/regulatory—information—search—fda—guidance—documents—completeness—assessments—type—ii-api—dmfs—under—gdufa—guidance—industry*

[18] *https://www.fda.gov—media—116004—download*

[19] *https://3www.fda.gov—inspections—compliance—enforcement—and—criminal—investigations—inspection—classification—data base*

[20] *https://www.fda.gov—industry—generic—drug—user—fee—amendments—enhanced—accountability—reporting*

[21] *https://www.fda.gov/about—fda—user—fee—reports—user—fee—five—year—financial—plans*

[22] *https://www.fda.gov/drugs—news—events—human—drugs—financial—transparency—and—efficiency—prescription—drug—user—fee—act—biosimilar—user—fee—act—and*

gram and whether corresponding outputs could be applied to the GDUFA program to meet the monitoring and reporting of resource needs of the program.[23] As discussed below, industry and FDA agreed to implement a CPA in GDUFA III.

GDUFA III Reauthorization

The accomplishments under GDUFA II continued to foster a strong generic drug market for the American public. For example, there are generic versions of the ten most prescribed medications by total prescriptions in 2020. Despite this success, the average first-cycle approval rate remains around 15 percent. While progress is improving in the approvals of complex generics, about 30 percent of active reference products, that do not have generic competition, are complex products. Therefore, the GDUFA III negotiations focused on building on the successes of GDUFA II by proposing new processes and procedures to achieve earlier cycle approvals and enhancing the pre-ANDA program.

GDUFA III Overview

ANDA Assessments

The GDUFA III commitment letter proposes minimizing issuance of complete response letters (CRL) which, as described above, are letters from FDA to an applicant detailing the deficiencies in an application that must be resolved prior to approval, by:

- Utilizing "Imminent Actions" whenever possible to approve an application within 60 days after the goal date if there is a small issue to resolve or a pending expiration of a reference listed drug patent or exclusivity within that time period;
- Extending goal dates when there is a minor issue that can be resolved within 3 months of the original goal dates, e.g., addressing a labeling issue; this includes changes in labeling review processes to provide more resources to address late-cycle labeling changes;
- Providing the opportunity to extend the goal date by 6–10 months, depending upon the type of ANDA and need for a pre-approval inspection, if an applicant can respond to a major deficiency before the original goal date; such extensions could shorten the overall time to approval.

The commitment letter also seeks to refine the Pre-Facility Correspondence process for priority ANDAs to focus on the information that is available from applicants' pre-ANDA submissions to inform FDA's decision regarding the need for a preapproval inspection, to expand opportunities for applicants to use this process.

Another commitment is to increase opportunities for timely regulatory feedback through the expanded use of controlled correspondence to include, for example, questions related to generic drug development after receipt of a CRL, in addition to the opportunity for a post-CRL teleconference.

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[23] *https://fda.report—media—140656—Independent—Evaluation—of—the—GDUFA—Resource—Capacity—Planning—Adjustment—Methodology—0.pdf*

Drug Master Files and Manufacturing Facilities

For drug master files the commitment letter proposes expanding opportunities for early assessment of DMFs before certain priority ANDAs are submitted and between review cycles to increase the likelihood that the DMF will be adequate at the same time as the associated ANDA and thereby promote earlier cycle approvals. In addition, there will be new goal dates for FDA's response time for manufacturing questions submitted by a sponsor using controlled correspondence after their ANDA is approved.

While most facilities are compliant with Current Good Manufacturing Practice requirements, a small number of ANDA manufacturing facilities are not able to gain approval to produce ANDAs for the U.S. market due to significant violations identified during an inspection. To assist manufacturers in resolving such violations more expeditiously, under the GDUFA III commitment letter, eligible generic drug facilities could request a Post-Warning Letter Meeting to obtain preliminary feedback from FDA on the adequacy and completeness of their corrective action plans. Once a facility has completed appropriate remediation action and FDA agrees that the next step is a facility reinspection, there would be a goal around the timing for such reinspection.

Pre-ANDA Program and Regulatory Science

The GDUFA III commitment letter proposes to continue to enhance regulatory science and expedite complex generic drug development by providing additional enhancements to the programs. In addition to the GDUFA II goals around PSGs for new molecular entities, the GDUFA III commitment letter would establish goals around PSGs for NDAs for complex drug products approved during GDUFA III. FDA would also commit to improving transparency regarding the timing for upcoming new and revised PSGs, including the prioritization of PSG development. The commitment proposes allowing qualified ANDA applicants or potential applicants to request a PSG teleconference or meeting to obtain Agency feedback on the potential impact of a revised PSG recommendation(s) on ongoing in-vivo bioequivalence studies.

The meeting types provided under GDUFA II are being enhanced and expanded. The GDUFA III commitment letter proposes providing qualified ANDA applicants with the new option for an Enhanced Mid-Cycle Review Meeting to receive scientific advice with the goal of resolving a more significant scientific deficiency in a single review cycle, with appropriate goal date extensions. The proposal also includes providing qualified ANDA applicants a post-CRL Scientific Meeting in which the Agency may provide scientific advice on possible alternative approaches to address deficiencies related to establishing equivalence identified in a CRL.

Finally, the commitment letter proposes setting goal dates for suitability petitions, under which generic drug applicants can submit ANDAs for drug products that differ from an approved brand drug in new dosage form, strength, route of administration, or active ingredient for products with a combination of more than one active ingredient. These petitions usually are submitted in response to market demand that is not met by an approved brand

product. These goal dates would be established starting in fiscal year 2024.

Hiring

To provide the capacity needed to successfully implement the new commitments, while maintaining current performance, the GDUFA III proposal recommends increasing fees to fund 128 new FTEs (to be hired in fiscal year 2023). Under GDUFA III, the Agency will provide transparency with respect to hiring in its 5-year financial plan reports.

Enhancement of Management of User Fee Resources

GDUFA III proposes to enhance the operational agility of the GDUFA program and management of user fee resources through further maturation of the Resource Capacity Planning (RCP) capability and a legislative proposal to establish and implement a Capacity Planning Adjustment (CPA) to be used in annual fee-setting annually starting in fiscal year 2024. The CPA would generally allow for up to a 3-percent increase in inflation-adjusted target revenue for the fiscal year if there are forecasted, sustained increases in workload. This legislative proposal would also eliminate the statutory final year adjustment and replace it with authority for an operating reserve adjustment, to provide the Agency with the option of increasing revenues to help ensure adequate resources in the case of significant under collection of fees or other disruptions in funding. This operating reserve adjustment would allow the Agency the option to increase fees to maintain an operating reserve of 8–10 weeks' worth of carryover user fees. If projected operating reserves exceed 12 weeks of operating costs, FDA would be required to reduce fees for that fiscal year to reduce the operating reserve to no more than 12 weeks of carryover fees. FDA would provide the rationale for the CPA and operating reserve adjustments in the annual Federal Register notice publishing fee rates for that fiscal year. GDUFA III would continue financial transparency by publishing a 5-year financial plan and holding a public meeting to discuss the plan and other financial commitments every fiscal year.

BsUFA

Over the past decade, new biological products have led to significant clinical improvements for patients who have serious and life-threatening medical conditions including cancer, rheumatoid arthritis, and diabetes. It is important for the public health of the U.S. population to have access to safe, effective, and affordable biological products. Biosimilars provide more options for patients, and competition has the potential to lower treatment costs, enabling greater access for more patients. FDA is fully engaged with the development and approval of biosimilar and interchangeable biosimilar products and is applying a scientifically rigorous review process to ensure these products meet approval standards, in conjunction with outreach to prescribers and patients. Healthcare providers and patients consistently emphasize that FDA's approval of biosimilars should provide assurance that they provide the same treatment benefits as the originator, or reference product. FDA is

committed to providing this assurance and recognizes its importance to the future success of the biosimilars program.

Biologics Price Competition and Innovation Act of 2009 (BPCI Act)

Biological products are generally made from living organisms and usually consist of large, complex molecules that cannot be easily copied, in contrast to "small molecule" drugs that are produced through chemical processes and are easier to copy as "generic" drugs. The BPCI Act established an abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological reference product. A biosimilar product is one that is highly similar to the reference product notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences in terms of safety, purity, and potency. An interchangeable product is a biosimilar product that meets the additional requirement of demonstrating that the product is expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once to a patient, the risk in terms of safety or diminished efficacy of alternating or switching between the biosimilar and reference product is not greater than the risk of using the reference product without such alternation or switch.

The abbreviated approval pathway permits a biosimilar application to rely, in part, on FDA's previous determination that the reference product is safe and effective, saving the applicant time and resources and thereby encouraging competition and potentially lowering healthcare costs.

FDA Biosimilar Approvals—Progress Continues

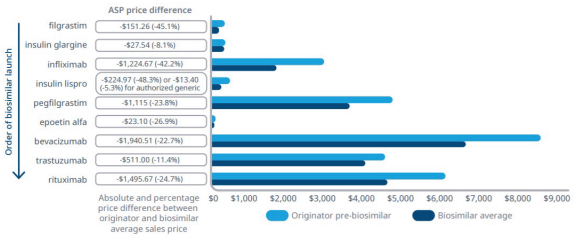
FDA approved the United States' first biosimilar product, Zarxio, on March 6, 2015, 2 years prior to the most recent reauthorization of the Biosimilar User Fee Act (BsUFA II) under the FDA Reauthorization Act of 2017 (FDARA). When BsUFA II was enacted, there were only five biosimilar products approved for four reference products. During BsUFA II the number has grown to 33 biosimilars for 11 reference products, including two interchangeable biosimilars as of April 18, 2022.[24] A recent analysis by IQVIA provides data on potential savings with biosimilars.[25]

[24] *https://www.fda.gov—drugs—biosimilars—biosimilar—product—information*

[25] *https://www.iqvia.com—media—iqvia—pdfs—institute—reports—iqvia—institute—biosimilars—in—the—united—states.pdf*

Absolute savings from biosimilars vary, with larger savings from more recent launches where originators were more costly

Exhibit 12: Originator and Mean Biosimilar Average Sales Price (ASP) in US$, July 2020



Source: CMS ASP Jul 2020 accessed Sep 2020; IQVIA National Sales Perspectives, Jul 2020; IQVIA Institute, Sep 2020

For example, the cost of insulin products is a barrier to patients obtaining sufficient supply of this essential drug. Interchangeable biosimilars, like generic drugs, may be substituted for the reference product without the involvement of the prescriber, depending on state pharmacy laws. Pharmacy level substitution may further reduce costs, helping to increase patient access. On July 28, 2021, FDA approved the first interchangeable biosimilar insulin product, indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee (insulin glargine-yfgn) is both biosimilar to, and interchangeable with (may be substituted for), its reference product Lantus (insulin glargine), a long-acting insulin analog. On December 17, 2021, FDA approved a second biosimilar to Lantus: Rezvoglar (insulin glargine-aglr). These two biosimilar products move the needle forward in our common goal to help ensure increased access to a critical therapy in the treatment of diabetes for Americans who depend on insulin.

Biological products for the treatment of inflammatory conditions greatly improve patients' lives. However, treatment can be costly—for example, in 2021, the cost of a year's supply of Humira was approximately $77,000; equating to about $3,000 per syringe.[26] Currently, the seven approved biosimilar products to Humira are not on the market, but some could enter the market in 2023.[27] One of these biosimilars was approved as an interchangeable biosimilar product. On October 15, 2021, Cyltezo (adalimumab-adbm), originally approved as a biosimilar in August 2017, was approved as interchangeable with its reference product Humira (adalimumab) for Cyltezo's approved uses. Cyltezo is the first interchangeable monoclonal antibody.

BsUFA II—Fulfilling Our Commitments

We are currently in the final year of the BsUFA II program. BsUFA has enabled FDA to implement a new review model and expand staff capacity to provide increased communication with com-

[26] House Committee on Oversight and Reform—AbbVie report: *https://oversight.house.gov—sites—democrats—oversight—house—gov—files—Committee percent—on percent—Oversight percent—and percent—Reform percent—percent—AbbVie percent—Staff percent—Report.pdf*

[27] AbbVie & Allergan, 2020 Annual Report on Form 10-K: *https://investors.abbvie.com/static—files/47512e94—a9a4–4035–8dbc–6eb59116bb05*

panies facilitating biosimilar product development. BsUFA II built upon the successes of BsUFA I and established an application review model like "the Program" established under PDUFA V for new molecular entity new drug applications and original biologics license applications. This new model is intended to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval. The main parameters of the Program include the following: 1) pre-submission meetings, 2) original application submissions, 3) Day 74 Letter, 4) review performance goals (10-month user fee clock starts at 60-day filing date), 5) mid-cycle communications, 6) late-cycle and advisory committee meetings, and 7) assessment of the Program. These changes contributed to the increase in approvals during the first cycle, reaching almost 70 percent during BsUFA II compared to 39 percent during BsUFA I.

Meetings and Collaboration

FDA made modifications to meeting processes and procedures as part of BsUFA II. We published a draft guidance "Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products"[28] and issued a final guidance on "Best Practices for Communication Between IND Sponsors and FDA During Drug Development".[29] As of January 3, 2022, there are close to 100 active biosimilar development programs and we received meeting requests to discuss the development of biosimilars for 47 different reference products. Because these communications are often opportunities to share information and provide critical advice (e.g., trial design, analytical similarity assessment, nonclinical studies, manufacturing, and facility issues), it is important that interactions be conducted efficiently and consistently, with clear, concise, and timely communication. Issuance of guidance on these topics is intended to further those goals and help to foster an environment where sponsors and FDA can work collaboratively during the biosimilar drug development process.

Strengthening Staff Capacity

The ability to hire and retain qualified staff is critical to facilitating the availability of new safe and effective biosimilars. The BsUFA II commitments supported this priority by strengthening FDA's staff capacity; modernizing the hiring system infrastructure; improving human resources capacity through use of a dedicated expert contractor; establishing a dedicated function for the recruitment and retention of scientific staff; and setting clear goals for hiring. In addition, FDA committed to conducting a comprehensive and continuous assessment of hiring and retention practices. This increase in staff capacity during BsUFA II facilitated the development of new regulations and guidance to clarify the biosimilar pathway and to support reviewer training and timely communication with sponsors. This included issuing guidances that are

[28] *https://www.fda.gov—regulatory—information/search—fda—guidance—documents—formal—meetings—between—fda—and—sponsors—or—applicants—bsufa—products—guidance—industry*

[29] *https://www.fda.gov/regulatory—information—search—fda—guidance—documents—best—practices—communication—between—ind—sponsors—and—fda—during—drug—development*

foundational to the biosimilar pathway. FDA has issued draft or final guidance for all guidances listed in the BsUFA II commitment letter.

Last, BsUFA II included goals related to the publication of information about biological products. Addressing these goals and commitments, in 2020, FDA released "The Purple Book: Data base of Licensed Biological Products,"[30] which is a searchable, online data base that contains information about FDA-licensed (approved) biological products, including biosimilar and interchangeable products and their reference products. The data base provides users with a public-facing data base that includes important information about biological products, including information about product presentations, strength, and dosage forms, in addition to other searchable and sortable data fields.

Independent User Fee Structure

Under BSUFA II, FDA successfully implemented an independent user fee structure based on BsUFA I program costs, along with other financial enhancements to improve FDA's ability to manage program resources and engage in effective long-term planning. FDA also implemented commitments to improve financial transparency and efficiency, including conducting an independent evaluation of BsUFA program resource management[31] and issuing a BsUFA 5-year financial plan with annual updates[32], in addition to the annual financial reports,[33] and annual public meetings to discuss program finances.[34]

BSUFA Reauthorization

The statute directs FDA to develop recommendations for BsUFA III for fiscal years 2023 through 2027. To develop these recommendations, FDA consulted with industry and public stakeholders, including scientific and academic experts, health care professionals, and patient and consumer advocates, as directed by Congress. In addition to meetings with industry organizations, FDA held two public meetings on November 19, 2020, and November 2, 2021, to obtain input from public stakeholders. To ensure transparency in this work the Agency has posted the meeting minutes, including the two public meetings and the 13 negotiation sessions with industry. The recommendations for BsUFA III were transmitted to Congress on January 12, 2022.

BsUFA III Overview

Based on successes of the BsUFA program, the BsUFA III commitment letter focuses on many of the top priorities identified by public stakeholders, regulated industry and FDA. The commitments build on the experience gained through the first and second iterations of BsUFA by expanding on existing successful enhance-

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[30] *https://purplebooksearch.fda.gov/*

[31] *https://www.fda.gov/drugs/development—resources—fiscal—year—2018—financial—management—evaluation—human—drug—user—fees—assessment—report*

[32] *https://www.fda.gov/about—fda—user—fee—reports—user—fee—five—year—financial-plans*

[33] *https://www.fda.gov—about—fda—user—fee—financial—reports/bsufa—financial—reports*

[34] *https://www.fda.gov/drugs/news—events—human—drugs—financial—transparency—and—efficiency—prescription—drug—user—fee—act—biosimilar—user—fee—act—and*

ments, refining elements from the existing program, and including new enhancements. Highlights of the proposed commitments are summarized as follows.

Enhancing pre-market review processes, procedures, and performance

BsUFA III proposes to retain the majority of existing review performance goals FDA and industry agree are working well in the program. With 33 approved biosimilar products to date and more anticipated, FDA and industry expect companies will submit more supplements to FDA during BsUFA III for these products and others that may be approved during BsUFA III. As such, BsUFA III proposes new supplement categories, review timelines and performance goals to expedite the review of certain supplements, including the review of safety labeling updates. In addition, this proposal seeks to improve communication and feedback during the development process by modifying two formal meeting types, introducing a new meeting type to focus on a narrower set of issues than other formal meetings to enable faster responses to industry, and introduces a new follow-up opportunity for sponsors to submit clarifying questions after meetings or "Written Response Only" correspondence to ensure sponsor's understanding of FDA feedback.

Enhancing biosimilar and interchangeable product development and regulatory science

BsUFA III proposes to continue the framework established in BsUFA II by incorporating best practices in FDA-sponsor communication through updates to relevant guidances, Manual of Policies and Procedures (MAPPs), and Standard Operating Policy and Procedures (SOPPs).

BsUFA III includes commitments for the Agency to:

- Issue guidance on FDA's thinking on the use of alternative tools to assess manufacturing facilities named in pending applications (incorporating best practices, including those in existing published documents, from the use of such tools during the COVID–19 pandemic);
- Notify sponsors in advance of facility inspections where FDA needs to see the product being manufactured; and
- Advance the development of review processes for biosimilar biological-device combination products by introducing new procedures and timelines for use-related risk analysis and human factor validation study protocols.

To further advance the development of safe and effective interchangeable biosimilar products, BsUFA III proposes a focused effort that includes issuing four foundational guidances for the development of interchangeable products; stakeholder engagement through a scientific workshop; and leveraging the new BsUFA III regulatory science program to advance product development, assist regulatory decisionmaking, and support guidance development for interchangeable biosimilar products.

As proposed, the BsUFA III regulatory science pilot program would be broadly applicable to biosimilar and interchangeable product development. The pilot program would focus on two demonstration projects: (1) advancing the development of interchange-

able products, and (2) improving the efficiency of biosimilar product development.

Continuing enhancements for management of user fee resources

Similar to PDUFA VII, BsUFA III proposes to continue to enhance management of user fee resources by advancing FDA's resource capacity planning function and adjustment methodology, including a third-party evaluation of the methodology by 2025. The proposal would continue financial transparency through issuance of a 5-year financial plan with annual updates and holding annual public meetings to discuss BsUFA finances.

Improving FDA's hiring and retention of key scientific and technical talent

To accomplish the goals set out in the proposed commitment letter, the Agency would hire 15 new employees for fiscal year 2023 and fiscal year 2024. Like PDUFA VII, BsUFA III proposes to further improve FDA's hiring and retention of key scientific and technical talent by providing transparency on hiring progress by reporting on progress toward meeting annual BsUFA III hiring goals on FDA's website and conducting a third-party assessment of FDA's hiring and retention.

Enhancing IT goals

Similar to PDUFA VII, BsUFA III proposes to enhance transparency of IT activities and modernization plans, including by publishing a data and technology modernization strategy. The proposal would also modernize the Electronic Submission Gateway.

MDUFA

Enacted by Congress in 2002, MDUFA is a user fee program through which medical device companies pay fees to FDA when they submit a request for marketing authorization, or certain other submissions, or register their establishments with FDA. The program includes commitments between the U.S. medical device industry and FDA to improve the predictability, transparency, and consistency of regulatory processes, which are intended to reduce the time for FDA to make a decision about whether to authorize marketing of a device. MDUFA has been reauthorized every 5 years since Congress first established the program in 2002. As the program has evolved, FDA and industry have successfully negotiated agreements to improve patient access to medical devices and streamline regulatory processes, all while assuring the safety and effectiveness of devices that patients and healthcare providers depend upon.

We have seen tremendous evolution and progress in FDA's medical devices program since inception of MDUFA. Prior to MDUFA enactment, FDA's devices program was in a far different place than the program we see today. We saw much longer review times, which led to less predictability and transparency for industry and patients. The investments made in the previous reauthorizations helped the MDUFA program make substantial progress. For example, we advanced more aggressive performance goals for 510(k) and premarket applications (PMA), including shared outcome goals; we added performance goals for Pre-Submissions (which provide an op-

portunity for a sponsor to obtain FDA's feedback prior to an intended submission such as an Investigational Device Exemption (IDE) or marketing application), and De Novo requests; as well as added process improvements for real world evidence, digital health, patient engagement, and use of consensus standards. As a result of these developments, we have seen an increasing number of innovators bring their devices to the U.S. first, before seeking to market them in other nations. We are seeing the pipeline of innovative new devices in the U.S. continues to become more robust, improving patient access to medical devices overall—with access being an important indicator of success for patients who may not have approved/cleared/marketed alternatives. It also demonstrates that a strong MDUFA agreement enables patients to have access to more innovative and better performing devices—and therefore more options—than at any other time in our history.

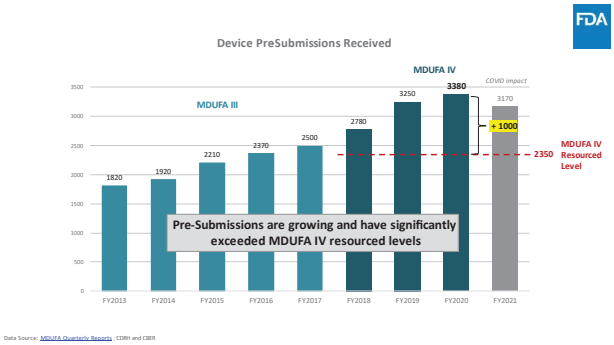
The draft MDFUA V reauthorization proposal was submitted to Congress on March 22, 2022. We expect to submit the final proposal following the close of public comments in April, and regret missing the statutory deadline to deliver the MDUFA V agreement this year. We take our obligation to provide the agreement to Congress in a timely manner very seriously, and know it is important for the Committees in both the House and Senate to have the opportunity to fully evaluate the agreement and engage with FDA and industry on the details because of how much is at stake, for FDA and our health care system. The deliberations on this agreement ran much longer than we intended, but it was critical that we took the time to deliberate and reach consensus on a strong, thoughtful agreement that assures the device program is appropriately resourced, and that we are supporting industry and innovators with a consistent, predictable, timely path to market for the safe and effective devices patients depend upon. We appreciate the patience of the Committee as we worked to reach an agreement that continues the progress made in the previous agreements toward advancement of medical device innovation, while maintaining FDA's standards. This is critical, as FDA and the device ecosystem face some of their greatest challenges. FDA's devices program continues to shoulder the unprecedented demands of the global COVID–19 pandemic, where the demand for medical devices has far exceeded anything we have seen in previous public health emergencies, while working hard to keep up with our MDUFA commitments as much as possible, and fulfill our ongoing mission of protecting public health and facilitating medical device innovation.

MDUFA IV

The MDUFA IV agreement enabled FDA to continue making progress on reducing review times and bringing devices to patients more quickly, while also enabling FDA to move forward in critical areas including advancing our work to support innovation in digital health, strengthening our partnership with patients, enhancing our program to adopt consensus standards, and improving our ability to leverage real world evidence toward regulatory decisions. In terms of review goals, we had a strong performance during the first half of MDUFA IV, continuing to meet and exceed performance goals, working to reduce the time for patients to have access to

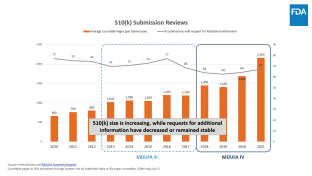
safe, new, innovative devices. In fiscal years 2018 and 2019, FDA achieved all of our submission review goals, met 21 of 24 performance enhancement goals, and FDA and industry met three of four shared outcome goals. Though not perfect, this performance evidences a continually robust pipeline for new and innovative devices, which is a positive condition for U.S. patients and our health care providers on the front lines. And with a robust pipeline comes an increase in workload, which reached some of its highest levels in key areas and substantially impacted our Center.

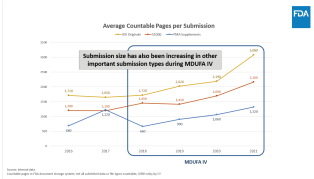
- Pre-Submission requests grew substantially beyond what was resourced in MDUFA IV. MDUFA IV assumed that Pre-Submission volume would hold steady at 2,350 submissions per year. In fact, FDA received over 3,000 more Pre-Submissions than we were resourced to review in MDUFA IV, including more than 1,000 submissions in fiscal year 2020 alone. Growth in non-Breakthrough related Pre-Submissions was steady and linear for 7 years prior to the pandemic (2013–2020), while growth in Breakthrough-related Pre-Submissions has been much more significant, increasing by an average of about 40 percent each of the last 3 years (FY 2019-fiscal year 2021). With significant growth driven primarily by the popularity of the Breakthrough devices program, we expect to receive approximately twice as many Pre-Submissions per year by the end of MDUFA V than what was resourced in MDUFA IV.



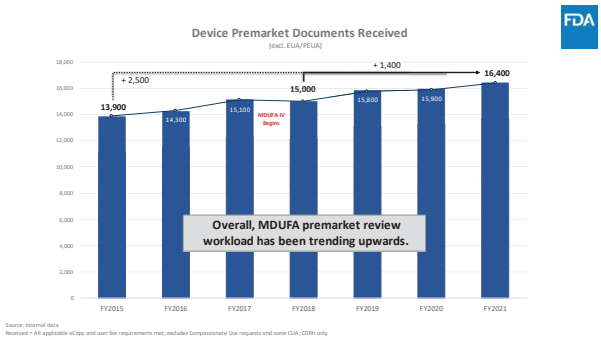
- Submissions have and continue to become increasingly complex and, as a result, review of premarket submissions has become more resource-intensive. This rise in complexity is evidenced in several ways
  - Throughout MDUFA III, the average size of a 510(k) submission held steady, at around 1,000 pages per submission. In MDUFA IV however, the average size of a510(k) has steadily and significantly increased, nearly doubling to an average of2,000 pages per submission in 2021. This increase occurred while FDA's requests for industry to provide additional information decreased or remained stable. This increase in submission size is not

just limited to 510(k)'s. Average submission size has also increased in other important submission types during MDUFA IV. For example, the average size of an Original IDE grew by 1,300 pages (from around1,700 pages per submission in 2018 to more than 3,000 pages in 2021) and the average size of a PMA Supplement doubled (from around 650 pages per submission in 2018 to more than 1,320 pages in 2021).





- FDA has approved or authorized record numbers of novel devices during MDUFAIV. In 2021, CDRH gave marketing authorization to 103 novel devices, an incredible achievement, especially during a time of increased demand on CDRH staff during the pandemic. Over the past decade, in fact, there were four times as many medical device approvals, authorizations, and clearances of novel technologies as a result of the innovative policies and approaches FDA has developed and implemented.
- Since fiscal year 2018, FDA has granted more than 600 Breakthrough device designations—and more than 200 in the last fiscal year alone (FY 2021). The majority of sponsors of these products go on to submit multiple additional requests for FDA feedback (via Pre-Submissions) shortly after their designation is granted, with roughly 1/3 submitting five Pre-Submissions or more. More than 50 percent of companies receiving Breakthrough designations are either small or startup companies (i.e., no or less than $1M in annual sales).
- FDA is also continuing to receive more premarket submissions overall than it has in previous years. For instance, in fiscal year 2015, we received nearly 13,900 total premarket submissions, and in fiscal year 2016 received nearly 14,300. In contrast, for fiscal year 2021, FDA received over 16,400. This is approximately a 20 percent increase (or ?2,500'submissions) since fiscal year 2015, and a 10 percent increase (or ?1,400 submissions)'since the start of MDUFA IV.



We also note another challenge of MDUFA IV was the rising payroll costs in CDRH and CBER, and the MDUFA inflation formula did not keep up. These payroll costs come from forces outside of the program's control—including government wide, mandatory cost-of-living adjustments; automatic "step" increases for employees; and increased contributions to the Federal retirement benefit. For CDRH, in fiscal year 2022, the accumulated payroll cost impact of these factors for the MDUFA program is $45.5M. However, CDRH received $8.7M from the MDUFA payroll inflation adjustment, leaving a gap of $36.8M. These increased costs likewise placed additional strain on the devices program.

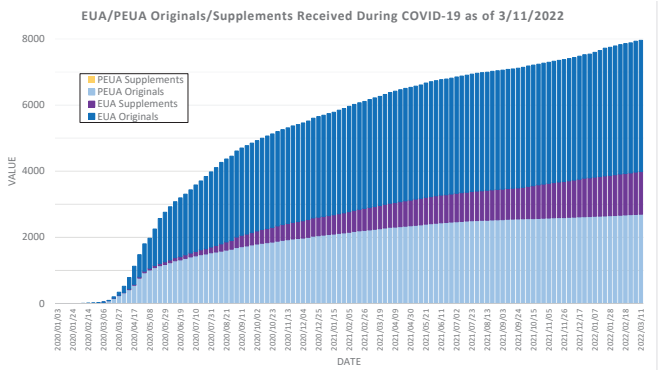
COVID–19

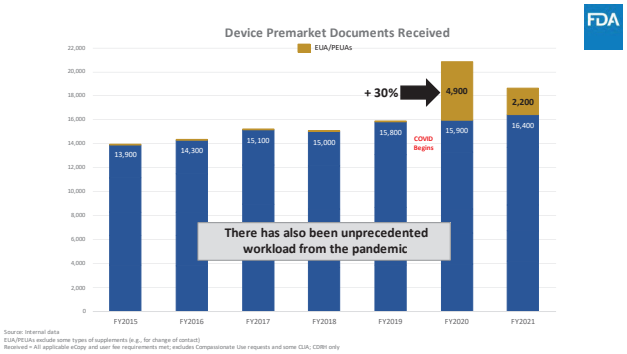
It is hard to overstate the impact the global pandemic has had on CDRH and the entire Agency, as it did for so many individuals, organizations, and communities around the world. Responding to this public health emergency (PHE) became central to our work and pushed us into a continuous all-hands-on-deck status, working oftentimes literally around the clock to facilitate the development and availability of pandemic-related devices as quickly and safely as possible. FDA's work to support access to devices for the COVID–19 response began in January 2020—before the PHE was declared in the U.S. and 2 months before the pandemic was declared worldwide—due to the immediate need for COVID–19 tests and testing supplies, collection kits, personal protective equipment (PPE), ventilators, and other devices. To help combat the COVID–19 pandemic, FDA and CDRH staff have continued to go well beyond normal operating procedures to help ensure the availability of appropriately safe and effective COVID–19-related devices as quickly as possible.

From early in the pandemic, CDRH has actively reached out to and engaged other government agencies, medical device developers and international regulatory agencies, among other stakeholders. CDRH continues to hold weekly virtual town halls with industry to address COVID–19 test development and validation, as well as additional webinars and town halls addressing other policies and questions including PPE, 3D printed swabs and manufacturing disruptions during the public health emergency. CDRH staff have also interacted frequently with test developers and manufacturers

through the Pre-Emergency Use Authorization (PEUA) process, including rolling reviews of information that helped to further expedite emergency use authorization (EUA) of critical medical devices for patients and health care professionals on the front lines. Since the beginning of the pandemic, CDRH has prioritized at-home tests, balancing speed with safety to ensure COVID–19 tests are appropriately accurate and reliable as supported by valid scientific evidence. CDRH has authorized 19 over-the-counter (OTC) at-home tests, resulting in hundreds of millions of additional OTC tests available monthly to American consumers. CDRH also took several additional steps, including: facilitating OTC COVID–19 test availability by issuing updated templates for EUA requests to streamline authorization of OTC tests; partnering with the National Institutes of Health (NIH) on the Independent Test Assessment Program (ITAP) to support FDA's evaluation of OTC COVID–19 tests that have the potential for manufacturing at significant scale, which resulted in five OTC authorizations of tests; and triaging our review efforts to focus on tests that ensure the biggest public health impact. We continue to grant EUA requests and take other actions, and we are proud that these contributions continue to help to facilitate the availability of critical devices and supplies for health care providers and patients.

We also saw innovators across the device ecosystem mount a remarkable response—medical device manufacturers large and small turning their production lines to different types of devices, and non-traditional manufacturers who came forward to manufacture devices for the first time—all to meet the needs of an unforgiving pandemic. Our team worked closely with them, night and day, to review EUA and Pre-EUA submissions, and the volume of EUA requests quickly surpassed (by several orders of magnitude) that of any prior PHE or emergency. It is important to appreciate that this enormous addition to our workload to review EUA and Pre-EUA submissions could not be supported by MDUFA funds. FDA engaged in an unprecedented effort to engage with sponsors from the outset, to provide regulatory flexibility where appropriate, and to handle the influx of EUA submissions along with a simultaneously increasing volume of MDUFA work. In doing so, FDA contended with a workload that far exceeded our capacity.





- FDA has received approximately 8,000 EUA and Pre-EUA requests for devices since January 2020 (including over 900 so far in fiscal year 2022), and continues to receive over130 EUA and PEUA submissions a month.
- To date, we have granted EUAs or traditional marketing authorizations to nearly 2,300medical devices for COVID–19, including 15-times more EUAs for this PHE than all other previous PHEs combined. This includes ventilators and novel devices such as extra corporeal blood purification devices, as well as novel indications for devices such as continuous renal replacement therapy devices, for which FDA had not issued EUAs before. All in all, CDRH has reviewed and cleared almost 1,400 510(k) devices for COVID–19 and future pandemics.
- We also issued 28 guidance documents (as well as 21 revisions) outlining policies to help expand the availability of medical devices needed in response to COVID–19.
- FDA also supported authorization and patient access to EUA devices and other devices through monitoring safety signals and medical device reports, publishing 23 letters to health care providers and 97 safety communications.

During 2020 and 2021, we also experienced an increase in conventional premarket submissions, as noted above. The enormous COVID–19-related workload taken together with the increase in our "regular" workload inevitably led to some delays and a backlog in the medical device review process.

FDA appreciates the impact this has had on companies across the country. This is why we have been transparent about the backlog of device submissions, issuing public communications and discussing expected impacts for sponsors during town halls, webinars, and in meetings with industry and other stakeholders. This is also why we have worked hard to reverse the backlog, for COVID–19 and non-COVID–19 devices, all while continuing to respond to the pandemic. Among other actions, we have adopted agile, interactive, and innovative approaches to review of EUA requests, published dozens of guidance documents and "EUA templates" to clarify agency recommendations and streamline review, implemented a

front-end triage process to identify devices that would have the greatest impact on public health, reallocated our staff and resources from product areas less impacted by COVID–19 to those with increased submission volume, and made use of overtime. We greatly appreciate the support from Congress, particularly in the form of supplemental funding we used to leverage contractors and to hire temporary staff to help review EUAs.

MDUFA IV Performance

The strain from the pandemic, as well as a workload that exceeded assumptions made in the MDUFA IV agreement, resulted in failure to meet some of our MDUFA IV goals. Specifically, we fell short of our goals, or are likely to, in the following areas:

- For fiscal year 2020, seven of 16 review goals[35] are still pending, six were met, and three goals were missed. The missed goals include:
  - The substantive interaction goals for:
    - 180-day PMA supplements, and
    - 510(k)'s.
  - The decision goal for Dual 510(k) and CLIA Waiver by Applications with no advisory committee input.
- For fiscal year 2021, seven of 16 review goals[36] are still pending, three have met the goal, and six goals were missed. The missed goals include:
  - The substantive interaction goal for:
    - Original PMAs and panel-track supplements,
    - PMA 180-Day supplements, and
    - 510(k)'s.
  - The decision goals for:
    - Original PMAs and panel-track supplements with no advisory committee input,
    - 180-Day PMA supplements, and
    - 510(k)'s.

FDA strives to meet all of our commitments, and we have built in additional transparency and accountability mechanisms in MDUFA V (which we will discuss in the next section). We also have statutory obligations to report to Congress on how we address and rectify missed performance goals. As we noted in the fiscal year 2021 MDUFA annual performance report, FDA will continue to prioritize COVID–19-related work to address the ongoing public health need for safe and effective medical devices. As the COVID–19 pandemic continues to evolve, the volume of new EUA submissions for COVID–19-related products should begin to lessen in non-in vitro diagnostic (IVD) offices. This reduction will allow FDA to begin focusing review resources back to MDUFA-related activities, bringing review performance back to "pre-COVID–19" levels for non-IVD offices. FDA has already begun to reverse submission delays, and review times have improved significantly. Submissions

[35] MDUFA IV Commitment Letter (fda.gov)
[36] MDUFA IV Commitment Letter (fda.gov)

for non-IVD products under review continue to generally meet MDUFA goals. The IVD Office is hiring, and will continue to hire, additional staff and contractors to address the increased volume of work in the office.

MDUFA V Reauthorization

MDUFA V supports both FDA's capacity to assess new medical device technologies and continues to provide a predictable, transparent path to market, while addressing critical resource gaps. The agreement strengthens our commitment to the foundation of the program—infusing more resources and people to review premarket device submissions. It also enhances accountability for FDA's performance and operations, and makes critical investments in the future of the program, to assure FDA has the resources to handle oversight and review of the robust pipeline of new technology and the innovations of tomorrow. It is an agreement that will ultimately lead to patients having timely access to new devices while upholding FDA's standards. Specifically, MDUFA V:

- Provides FDA with $1,783,931,700 over 5 years, helping assure the CDRH and CBER has resources it needs to handle a continually increasing workload resulting from strong innovation in the U.S., which impacted FDA before the COVID–19 pandemic.
- Supports improved performance across device types, to help assure U.S. patients have as rapid access as possible to innovative devices that are safe and effective.
- Increases accountability for the MDUFA program, to help assure critical transparency for industry, patients, and other stakeholders and helps assure FDA continues to meet its commitments under MDUFA V:
    - Including an innovative new mechanism for add-on payments, unique to the MDUFA program, where approximately $115 million will be available for "add-on" funding during MDUFA V. If specified goals for 510(k)'s, PMAs, De Novo requests, and Pre-Submissions are met in fiscal year 2023–2025, FDA would apply additional user fees in fiscal year 2025–2027 to support improvements in those goals.
    - Providing for annual hiring targets for new positions, for the first time in MDUFA's history. If the target is missed by a specified percentage, a formula will be applied to calculate an offset of registration fees to be applied in the next annual fee setting cycle.
    - Providing a cap for operating reserves in the carryover balance, which brings MDUFA into alignment with the other medical product user fee programs. If the carryover operating reserves grow beyond the prespecified level, additional funds will be sent back to industry in the form of offsets to registration fees.

- Retaining an independent contractor to conduct a MDUFA Workforce Data Assessment which would include:
  - Assessing current methodologies and data and metrics available to represent MDUFA full time equivalent (FTE) resources (e.g., FTE burn and positions engaged in MDUFA process activities), including the subset funded by user fees, for each applicable Center and office; and
  - Developing recommendations for improved methodologies and data and metrics to represent MDUFA FTE resources, including the subset funded by user fees.
- Providing additional transparency in the form of new reporting to industry and the public on use of MDUFA resources.

The agreement supports advancement of the patient perspective in regulatory decisions, continuation and expansion of the use of consensus standards to support device development and testing, leveraging of real-world evidence for regulatory decisionmaking, and enhanced coordination with international regulators, among other priorities.

MDUFA V pilots an innovative program to provide earlier, more frequent, and more strategic engagement with sponsors of products designated under the Breakthrough Devices Program and included in the Safer Technologies Program (STeP). The Total Product Lifecycle (TPLC) Advisory Program Pilot (TAP Pilot) will begin with a "soft launch" of up to 15 products in one CDRH Office of Health Technology (OHT) in fiscal year 2023, and will expand to enroll up to 325 products across multiple OHTs by the end of MDUFA V. The program has full accountability, starting with the fact that it is being implemented as a voluntary pilot where we will track over half-a-dozen metrics, and will assess the pilot program and provide a public report on progress during MDUFA V.

TAP will build upon lessons learned from these programs, as well as FDA's experience during the COVID–19 pandemic response, of engaging with sponsors through the pre-EUA process, which was critical for facilitating availability and accessibility of important products. The program will help to assure that device developers have a clear, predictable path to market such that patients have timely access to new devices. We believe it will help innovators avoid pitfalls in early product development, better ensure a clear, predictable path to market from development to bedside so that devices actually reach patients, and will continue to foster the innovation pipeline.

MDUFA V Overview

As we look toward efficient and expeditious implementation of our new agreement, FDA will continue to face significant challenges after two long years of a global pandemic that continues to significantly impact our day-to-day work:

- FDA continues to receive a high volume of EUA and Pre-EUA requests for tests and other devices.
- An increasing number of EUA-authorized devices are being submitted for full marketing authorization. This includes 15 EUA-authorized devices that have already received full marketing authorization and an additional 16 under review.
- We continue to see an increase in submissions for devices that do not have EUAs, but are seeking marketing authorization for use during COVID–19 and future pandemics. These include various types of PPE, tests and testing supplies, needles and syringes, ventilators and respiratory assistive devices, dialysis equipment, and infusion pumps, among others.

We are committed to continuing the return to "normal operations," but also know we will sustain some setbacks to our overall performance. This includes a continuing backlog of traditional device submissions for review. However, we have also begun to turn the corner—we have reduced the backlog of submissions by 45 percent. And even while in the middle of the pandemic, CDRH continued to authorize a record number of novel devices—over 100 each year—and we have been designating an increasing number of Breakthrough devices each year. FDA has demonstrated time and time again that we do our best to meet and exceed our commitments; and, the fact there are more safe and effective medical devices on the market—more options for patients—than at any other time in U.S. history is a testament to these ongoing efforts. This makes all the difference for U.S. patients, and relies in part on the resources our program has to fulfill our mission. The MDUFA V agreement will be instrumental in getting the program fully back on track, allowing patients to continue to benefit from the robust innovation pipeline for medical devices in the U.S. We appreciate patience and support as we worked toward an agreement and, with the support of Congress and the MDUFA reauthorization, we can continue to accelerate access to new technologies that meet FDA's regulatory standards.

CONCLUSION

User fees are critical to ensuring that FDA has the resources needed to conduct reviews in a timely fashion without compromising the Agency's high standards—all part of getting safe and effective medical products to patients sooner. The user fee programs are an example of what FDA, Congress, industry, and other stakeholders can achieve when working together toward the same goal. While we have made demonstrable progress in bringing drug and biological products and medical devices to market as quickly as possible, we know that more work remains to continue to enhance our review processes, including investing in the hiring and retention of scientific talent (particularly in areas of rapid growth such as cell and gene therapy), maximizing the use of new tools and regulatory science, and investing in a bioinformatics infrastructure to support the evolving needs of the programs. The reauthorization of PDUFA, GDUFA BsUFA, and MDUFA will allow FDA to build

upon the programs' demonstrated success, further benefiting patients and affirming our Nation's standing as a global leader in biomedical innovation.

Thank you for the opportunity to testify today. We will be happy to answer your questions.

QUESTIONS AND ANSWERS

RESPONSE BY PATRIZIA CAVAZZONI TO QUESTIONS FROM SENATOR CASEY, SENATOR HASSAN, SENATOR SMITH, SENATOR PAUL, SENATOR CASSIDY, SENATOR SCOTT, AND SENATOR TUBERVILLE

SENATOR CASEY

At our previous User Fee Agreements hearing with industry representatives, I asked about the role of patient voices in reviewing new therapies, particularly for rare diseases. I subsequently introduced S. 4071, the Helping Experts Accelerate Rare Treatments Act of 2022 with Senator Tim Scott. One of my aims with this legislation is to facilitate greater engagement with patients with rare diseases and specialized experts throughout the review process for therapies targeting their rare conditions. I have heard from patients with rare diseases who do not feel as though their voices are being heard, that the review and decision processes are sufficiently transparent, or that reviewers consistently have access to the specialized expertise necessary to appropriately consider these applications, due to the unique experiences of these patients and the challenges posed by necessarily small study population sizes.

Question 1. How can the FDA integrate more patient and expert clinician perspectives into the review process—from pre-application to post-approval—to better inform the entire review process, particularly when evaluating treatments for rare diseases?

Answer 1. FDA recognizes the importance of the patient and expert clinician perspective to inform drug development and regulatory decisionmaking. FDA incorporates the patient perspective in many ways, through patient listening sessions that focus on patient experiences, perspectives, and needs related to their health or a disease, patient focused drug development meetings that characterize the most significant symptoms of their condition and the impact of the condition on daily life and patients' approaches to treatment, and through public advisory committees that solicit independent expert advice where patients and expert clinicians often provide their expertise on rare diseases and conditions, which informs regulatory decisionmaking.

In addition, FDA convenes rare disease stakeholders in public meetings to discuss and provide recommendations on common issues in development of medical products across the spectrum of rare diseases. FDA also utilizes public dockets, through which the public can submit electronic and written comments on specific topics to FDA.

Patient experience data is an important part of the review process. Specifically, FDA reviewers assess a product's benefits and risks based, among other things, on data from patients. For patient experience data, this usually takes the form of Patient-Reported

Outcomes (PROs) or other types of Clinical Outcome Assessments (COAs). In clinical trials, PROs or COAs can be primary, secondary, or supportive endpoints. In addition, patient experience data can provide contextual or supporting information (e.g., tolerability, patient priorities or concerns). Thus, patient experience data is an important component of a marketing application.

Question 2. Are there opportunities to enhance CDER's review—for example, through improved biomarker or surrogate endpoint selection—by leveraging expertise beyond the FDA, such as the National Institutes of Health?

Answer 2. FDA is exploring those opportunities. Recently, in May 2022, FDA and the Duke-Margolis Center for Health Policy convened a virtual public workshop to present best practices and use cases for successfully bringing forward evidence generated through translational science for regulatory submissions. The workshop presented efforts from FDA, NIH, academia, patient groups, and industry to support surrogate endpoint and other biomarker identification and development for use in therapeutic development and regulatory submissions. In addition, it provided successful examples of using translational science in the development of therapeutics. These types of engagements foster interaction and discussion among stakeholders who are developing these tools and implementing them in therapeutic development programs.

SENATOR HASSAN

Question 1. In April 2022, the House Committee on Oversight and Reform released an interim report detailing their findings into these conflicts of interest. The report revealed that at least 22 McKinsey consultants worked on related projects for both the FDA and opioid manufacturers, some at the very same time. It is clear that McKinsey took advantage of gaps in FDA's contracting procedures by failing to disclose its potential conflicts of interest during the contract application process.

In light of these failures to disclose, is it appropriate for FDA to continue relying exclusively on contractors to self-disclose their conflicts?

Answer 1. FDA follows contracting regulations that apply across the entire Federal Government. FDA, as part of its solicitation and contract award process, includes Organizational Conflict of Interest (COI) language and clauses that outline what the contractor must do before, during, and after award. FDA relies on the Contractor to review the requirement and assure there is no actual or apparent COI on the part of either the Contractor's organization or its individual employees in performance of the contract. If so, the Contractor reports the potential COI and submits a mitigation plan for review and approval. This process is in compliance with the requirements regarding COI as delineated in the Federal Acquisition Regulations (FAR).

The FAR applies governmentwide and sets out consistent policies and requirements for Federal contracts. Modifying those requirements for one agency would interfere with that consistent approach.

SENATOR SMITH

Question 1. Senator Braun and I have introduced legislation, the Expanding Access to Low-Cost Generics Act, which would address the issue of generic drug products "parking" their 180-day market exclusivity and delaying entry to market. The Food and Drug Administration's fiscal year 2023 budget includes a proposal to address "parking" by specifying that the FDA can approve subsequent applications unless a first applicant begins commercial marketing of the drug to ensure that exclusivity lasts 180 days rather than multiple years. Dr. Cavazzoni, what is FDA's perspective on the approach to address parking outlined in our Expanding Access to Low-Cost Generics Act? Would FDA be supportive of the policy outlined in our bill? Would this policy help bring more low-cost generic drugs to market?

Answer 1. The *Expanding Access to Low-Cost Generics Act* would address the delayed access to generic drugs that currently occurs when unapproved first applicants who remain eligible for 180-day exclusivity block subsequent applicants who are otherwise ready for approval and marketing. FDA is supportive of the goals of this legislation, and the Agency anticipates it would bring low-cost generic drugs to the market more quickly than happens under current law in circumstances where a subsequent applicant who is otherwise ready for approval and marketing is blocked solely by an unapproved first applicant's eligibility for 180-day exclusivity (and certain other conditions are met).

Question 2. I have been tracking a new challenge brought by Genus Medical Technologies v. FDA, in which the D.C. Circuit required the FDA to regulate products that meet both the drug and device definitions as medical devices. I believe the FDA should have the discretion to regulate combination products as drugs or medical devices. Dr. Cavazzoni, how would clarifying the regulation of products subject to the Genus decision help avoid delays in approvals of drugs? Can you list out the categories of products that would be subject to the Genus decision? Is it important to include all of these categories of products in clarifying legislation?

Answer 2. We agree that FDA should be able to regulate combination products under the drug or device pathways, and the *Genus* decision does not impact our determination regarding which constituent part of a combination product provides the primary mode of action.

Legislation clarifying that all contrast agents, radiopharmaceuticals, and OTC monograph products are drugs (as they were regulated before the *Genus* decision), would help avoid delays in approvals of these products. These categories capture nearly all the products that may be impacted by *Genus*. The one category of products not included in this list would be certain ophthalmic products that prior to *Genus* were regulated as drugs, but post-*Genus* would be regulated as drug-led combination products. We do not think it is necessary to clarify that these should be regulated as drugs instead of drug led combination products, because for the most part, this change is not likely to have a significant impact on these products, as explained in our March 2022 Guidance entitled *Certain Ophthalmic Products: Policy Requiring Compliance with 21 CFR*

Part 4. Additionally, there may be a few other products that do not fall within the categories described above, that may transition from being regulated as drugs to being regulated as devices as a result of the *Genus* decision. However, without expressly restoring the discretion FDA exercised prior to the *Genus* decision, it is not likely feasible to ensure that no products transition from being regulated as drugs to being regulated as devices as a result of *Genus*.

Question 3. I have been working with Senator Cassidy on a proposal that would accelerate the therapeutic equivalence (TE) rating process for complex generic drugs. I appreciate the FDA's willingness to work with us on this policy proposal. Following up on your comments on the TE process during the hearing, I had some additional clarifying questions.

Question 3(a). Does the 505(b)(2) pathway serve as a suitable pathway for complex generic products?

Answer 3. The 505(b)(2) pathway is generally not an appropriate pathway for a drug product that is a duplicate of another approved drug product, including a complex drug product, that is eligible for approval under section 505(j) of the FD&C Act. FDA generally refuses to file a 505(b)(2) NDA for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the FD&C Act. See 21 CFR 314.101(d)(9). However, in certain circumstances where FDA is unable to obtain information needed to ensure that a product is safe and effective because of the constraints of the 505(j) pathway and our current regulations, a 505(b)(2) NDA may be appropriate.

Question 4. Has the FDA already approved and provided TE ratings for complex generics via the 505(b)(2) pathway? What additional information is provided in the subsequent citizen petitions?

Answer 4. FDA has provided TE ratings for products approved via the 505(b)(2) pathway. However, the 505(b)(2) pathway is not designed to provide the information needed for the Agency to make a TE evaluation at approval. Rather, in approving a 505(b)(2) NDA, FDA makes a finding that the 505(b)(2) NDA meets the statutory standards for approval, including those for safety and substantial evidence of effectiveness. The statutory and regulatory requirements for approval of a 505(b)(2) NDA are not aligned with the criteria for establishing therapeutic equivalence, and 505(b)(2) applications currently are not required to submit to FDA all the information needed to make these TE evaluations. For example, in order to a make TE evaluation FDA must determine, among other things, that the relevant products are bioequivalent in order to find the products to be therapeutic equivalents, but there is no statutory, regulatory, or scientific requirement that 505(b)(2) NDAs must establish bioequivalence to another listed drug as a requirement for approval. There are also many different types of 505(b)(2) applications, and the evidence needed to make a TE evaluation for these products can vary. For more complex 505(b)(2) NDAs (e.g., drug-device combination products, products containing complex active ingredients), FDA would need to consider different scientific and regulatory issues in order to make a TE evaluation than those scientific and regulatory issues that were necessary to consider in determining whether the 505(b)(2) NDA met the applicable legal

and regulatory requirements for approval. In general, a citizen petition for a TE evaluation would need to include information regarding the pharmaceutical equivalence and the bioequivalence of the drug product approved in a 505(b)(2) NDA and another listed drug product. The exact information to demonstrate these factors would likely differ depending on the complexity of the product involved.

In contrast, the 505(j) pathway is designed to provide the data and information needed for a TE evaluation to be made at approval.

Question 5. What resource demands would be placed on FDA if Congress directed FDA to make a TE determination at the time of approval rather than through a separate citizen petition process? How can Congress address these resource demands?

Answer 5. FDA does not currently make TE evaluations for 505(b)(2) NDAs at the time of approval. Because the statutory and regulatory requirements for approval of a 505(b)(2) NDA are not aligned with the criteria for establishing therapeutic equivalence, FDA would need to consider different scientific and regulatory issues to make a TE evaluation than those scientific and regulatory issues that were necessary to consider in determining whether the 505(b)(2) NDA met the applicable legal and regulatory requirements for approval. In addition, 505(b)(2) NDAs currently are not required to submit to FDA all the information needed to make a TE evaluation at the time of approval, meaning that FDA might not have all the necessary information to make a TE evaluation at the time of approval or 505(b)(2) applicants might have to generate additional information beyond that currently required by the statute and regulations to obtain a TE evaluation at the time of approval. As a result, we anticipate that there would be additional resource demands placed upon FDA if Congress directed the Agency to make TE evaluations for 505(b)(2) NDAs at the time of approval. The extent of those additional resource demands would likely depend, in part, on whether Congress directed FDA to make TE evaluations for all 505(b)(2) NDAs or only a subset of 505(b)(2) NDAs, as TE evaluations for more complicated 505(b)(2) NDAs would likely be more resource intensive. In addition, resources would be required for FDA to make recommendations on the type of information that should be submitted with a 505(b)(2) application to allow for a TE evaluation in specific circumstances.

SENATOR PAUL

Question 1. FDA recently released a direct-to-final guidance document changing the regulatory standard for ophthalmic drugs packaged with eye cups, eye droppers, or other dispensers to treat them as combination products. These products were previously regulated pursuant to 21 C.F.R. 200.50, which stated that the eye cups, eye droppers, or other dispensers were part of the drug product and not device components. FDA stated in its guidance that it was implemented with immediate force and effect-and no opportunity for notice and comment—"given the urgency of these issues following the decision of the U.S. Court of Appeals for the District

of Columbia Circuit in Genus Medical Technologies LLC v. U.S. Food and Drug Administration [Genus Decision]."

Even though the Genus decision pertained only to medical imaging products, FDA appears to have conveniently expanded that opinion to other types of medical products. In doing so, FDA revoked a regulation that has been in place since 1975 with the infrequently used mechanism of direct-to-final guidance depriving the public of the notice and comment process. Please explain why FDA felt that the Agency had the authority to revoke a regulation through guidance, which is non-binding and does not have the force and effect of law, rather than revising or revoking its regulations through notice and comment rulemaking. Further, please explain why FDA concluded that the Genus decision applied to 21 C.F.R. 200.50, and why the Agency felt it was impossible to allow for notice and comment on the guidance document issued.

Thank you.

Answer 1. Although the product at issue in Genus involved a medical imaging product, the court in the Genus decision stated "[e]xcepting combination products, devices must be regulated as devices and drugs—if they do not also satisfy the device definition—must be regulated as drugs." In implementing the Genus decision, FDA determined that the language in 21 CFR § 200.50(c) indicating that eye cups, eye droppers, and other dispensers intended for ophthalmic use are regulated as drugs when packaged with ophthalmic drugs was made obsolete, because these articles meet the device definition in section 201(h) of the FD&C Act.

In addition, we do not believe the change from regulating certain ophthalmic products as drug-led combination products rather than drugs is likely to have a significant impact on these products. As we explained in our March 2022 Guidance entitled Certain Ophthalmic Products: Policy Requiring Compliance with 21 CFR Part 4, we made the determination that prior public participation for this guidance document was not feasible or appropriate because FDA needed to communicate its compliance policy for certain ophthalmic products in a timely manner given the urgency of these issues following the decision of the U.S. Court of Appeals for the District of Columbia Circuit in Genus. However, even though we did not provide an opportunity for prior public participation, the guidance remains subject to comment in accordance with FDA's good guidance practices (GGP) regulation, and FDA will consider all comments received and determine whether revisions to the guidance document are appropriate. To date, we have not received any comments on the guidance in the docket.

SENATOR CASSIDY

Question 1. In recent months, FDA has issued more Complete Response Letters (CRLs) than approvals of applications for drugs to treat patients with chronic kidney disease [including CRLs on veverimer, taurolidine, tenapanor, roxadustat, bardoxolone and vadadustat]. How is FDA applying its benefit/risk framework to new drugs to treat this chronically ill patient population at high risk of serious cardiovascular and other complications, and working

with drug developers to ensure there are clear rules of the road to demonstrate safety and efficacy?

Answer 1. FDA recognizes that patients with chronic kidney disease have significant unmet medical needs that would benefit from novel safe and effective therapies. Since 2012, FDA has been a close partner with the American Society of Nephrology in a public-private partnership, the Kidney Health Initiative (KHI), with a mission to catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases. CDER, CBER, and CDRH have all been active participants in this partnership.

FDA meets with sponsors regularly, including those developing drugs to treat patients with chronic kidney disease, to provide advice regarding the design of a development program that would have the potential to generate the data needed to demonstrate that a drug is safe and effective.

Although FDA is not able to provide specific comment on unapproved applications, it is important to note that a marketing application might not be approved for a number of reasons. To the extent that a deficiency may relate to a determination that a drug has not been shown safe for a particular use, FDA applies a structured benefit-risk assessment framework, which involves making an informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to managing risks). This assessment takes into account the evidence of safety and effectiveness submitted by a sponsor in an application as well as many other factors, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks.

Question 2. Historically, the nephrology division at the FDA had one of the lowest rates of new drug applications submitted, particularly compared to oncology and cardiology. How does the FDA ensure that the legal standards are being applied equally by each division?

Answer 1. Many drug products for kidney diseases are regulated by the same division as those for heart disease (currently, the Division of Cardiology and Nephrology; formerly, the Division of Cardiovascular and Renal Products); FDA does not believe there is a different application of legal and regulatory standards within that division that would be responsible for differences in the number of submissions across these therapeutic areas. Instead, a variety of factors would be expected to influence the level of interest product developers may have in any given therapeutic area. A key driver of interest in drug development is often the advancement of scientific knowledge about the pathophysiology of disease; for example, as scientific research led to increasingly specific understanding of how certain cancers develop and grow, novel specific drug targets were revealed that allowed for a dramatic increase in interest in drug development for the field of oncology. Furthermore, scientific advances often generate the information needed to support

novel surrogate endpoints for use in clinical trials, especially for diseases that progress slowly.

As an example of FDA's involvement in facilitating drug development in kidney disease through advancing the science, FDA nephrologists co-led a project of the aforementioned Kidney Health Initiative (KHI) to identify endpoints that could be used as a basis for approval for IgA nephropathy, a disease for which there had been little progress in its treatment with no licensed or approved therapies. Collaborating with an international group of academic and industry scientists in the pre-competitive space, a review of the available evidence led to support for the use of a surrogate endpoint in this disease; in December 2021, FDA approved Tarpeyo (budesonide), using accelerated approval, for certain patients with IgA nephropathy on the basis of the surrogate endpoint supported by the KHI project.

Examples of drug approvals during 2021 that are important to patients with kidney disease include Lupkynis (voclosporin) to treat active lupus nephritis; Farxiga (dapagliflozin) to reduce the risk of kidney and heart complications in adults with chronic kidney disease at risk of progression; Kerendia (finerenone) to reduce the risk of kidney and heart complications in chronic kidney disease associated with type 2 diabetes; and Korsuva (difelikefalin) to treat moderate-to-severe itching associated with chronic kidney disease in adults undergoing hemodialysis. With advancements in the science of kidney diseases, FDA is hopeful that additional safe and effective therapies will be discovered to help patients with chronic kidney disease.

Question 2. A pillar of the PDUFA VII commitment letter is greater communication between FDA and drug sponsors to ensure that drug development programs have clear metrics, including for safety and clinical end points. How will these new commitments reduce unexpected analyses or standards introduced late in the development or application process for therapies developed to treat patients with kidney disease?

Answer 2. As noted, one of the goals for PDUFA VII commitments is to increase communication between FDA and sponsors to enable more effective and efficient drug development, including for drugs intended to treat kidney disease. A few examples include:

Question 3. Rare Disease Endpoint Advancement (RDEA) pilot program: endpoint development for rare diseases has been historically challenging due to lack of regulatory precedent, small trial populations, and limited understanding of disease natural history. To help address these challenges, the new pilot program is intended to provide a mechanism for sponsors to have increased, focused, and repeated interactions and communication with FDA to identify better ways to develop novel clinical endpoints for rare diseases, including rare kidney diseases. The learnings from this pilot will be shared with the public to promote innovation and evolving science that can advance the development of novel endpoints and methodologies for use in rare disease clinical trials.

Question 3(a). Communicating Anticipated Postmarketing Requirements (PMRs): to provide more predictability in the marketing application review stage, PDUFA VII includes a

new communication timeline for anticipated PMRs. This timeline is based on earlier assessment of the product safety data, and the timeline also allows for thoughtful consideration of any anticipated postmarketing studies that may be required.

Question 3(b). Type D and INTERACT meetings, Follow-up Opportunities: The new Type D meeting allows for focused discussion of critical issues in a sponsor's drug development program and for timely feedback from FDA. INTERACT meetings allow for early interaction with the Agency, before IND-enabling studies are conducted, to discuss issues that may be critical to the success of those studies, thus potentially reducing uncertainty and wasted resources. Finally, the follow-up opportunity provides a chance for sponsors to clarify their understanding of feedback received during a formal meeting with the Agency. This should also help to reduce unexpected issues later in development.

Answer 3. There are many other opportunities for sponsors to engage with FDA to obtain recommendations for a robust drug development program. While these examples of increased communication are intended to lead to increased predictability in drug development and review, it is important to point out that it is always possible that scientific questions could arise during our independent review of the full data sets that will generate a need for further analyses and engagement with the applicant, for example, on discovery of an unexpected safety event.

Question 4. Another pillar of the commitment letter is building on a focus of Patient Focused Drug Development to ensure that the patient voice in incorporated into drug development decisionmaking. How can we ensure that FDA takes into consideration patient preferences and potential acceptability of tradeoffs between treatment benefit and risk outcomes in high risk diseases like kidney disease?

Answer 4. FDA recognizes that the patient and expert clinician perspectives may be very important to inform drug development and regulatory decisionmaking. FDA provides opportunities to incorporate the patient perspective in many ways, including through patient listening sessions that focus on patient experiences, perspectives, and needs related to their health or a disease, and patient focused drug development meetings that characterize the most significant symptoms of their condition and the impact of the condition on daily life and patients' approaches to treatment. Some patient focused drug development meetings relevant to kidney disease have focused on: Alport Syndrome, focal segmental glomerulosclerosis (FSGS), C3 glomerulonephropathy, IgA nephropathy, membranous nephropathy, and primary hyperoxaluria. FDA also receives input through public advisory committees that solicit independent expert advice where patients and expert clinicians often provide their expertise on the diseases and conditions under discussion, which informs regulatory decisionmaking.

In addition, FDA convenes stakeholders in public meetings to discuss and provide recommendations on common issues in development of medical products across the spectrum of diseases. For example, in December 2020, FDA and the National Kidney Foundation co-sponsored a scientific workshop on clinical trial considerations in developing treatments for early stages of chronic kidney disease. A survey of patients, which solicited how much risk versus potential benefit they would be willing to accept, informed the discussions at this workshop.

Patient experience data may play an important role in the review process. Specifically, FDA reviewers assess a product's benefits and risks based, in part, on data from patients. For patient experience data, this can take the form of Patient-Reported Outcomes (PROs) or other types of Clinical Outcome Assessments (COAs). In clinical trials, PROs or COAs can be primary, secondary, or supportive endpoints. In addition, patient experience data can provide contextual or supporting information (e.g., tolerability, patient priorities or concerns). Patient experience data is frequently a valuable source of data in a marketing application.

SENATOR SCOTT

Question 1. Patients have expressed concerns that not all review divisions within FDA understand or apply the accelerated pathway appropriately. Some have even likened the experience to that of a "lottery" as to whether they'll be assigned a division with experience in ultra-rare conditions with well under 20,000 patients in the U.S.—and oftentimes only 2,000 or even 200 patients.

> *Question 1(a)*. How is FDA using external expertise to appropriately make risk-benefit decisions for rare and ultra-rare diseases when safety is established, there are no other treatment options, and the condition is life threatening or significantly impacting quality of life?

Answer 1. FDA recognizes that there is significant unmet need for patients and families living with rare diseases as most rare diseases do not have approved therapies at this time. As further discussed below, these circumstances are considered and incorporated into FDA's approach to rare diseases, regardless of the regulatory pathway used or available for a particular development program.

It is important to understand that FDA considers safety and clinical benefit in its review and this benefit-risk assessment takes into account the seriousness of the disease. Benefit-risk assessment is integrated into FDA's regulatory review of marketing applications. The benefit-risk assessment includes many factors, such as the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be needed. As articulated in our 2019 draft guidance that addresses demonstrating substantial evidence of effectiveness,[1] FDA recognizes that some patients and their caregivers are willing to accept less certainty about effectiveness in return for earlier access to much

[1] *https://www.fda.gov/media/133660/download*. When finalized, this will represent FDA's current thinking on this issue.

needed medicines. For example, for a life-threatening disease without any available treatment, FDA might accept the results of adequate and well-controlled investigations with less rigorous designs, such as historically controlled studies. FDA has approved many drugs for rare diseases by applying these principles, using both traditional and accelerated approval pathways, when there is evidence that the drug is effective. Importantly, rare disease drug development spans therapeutic areas. FDA has mechanisms and initiatives, such as policy councils and the Rare Diseases Team, to facilitate consistency across divisions around rare disease product development considerations, such as the use of accelerated approval and considerations related to regulatory flexibility.

FDA's clinical review staff take advantage of a multitude of resources to gain knowledge on rare diseases when the agency determines such advice would be helpful as FDA considers the risks and benefits of medical products, including those intended for rare diseases based on the statutory definition (i.e., <200,000 in the U.S.).

Development and review of rare disease applications frequently involves challenging considerations that may benefit from discussion with external experts, such as at advisory committee meetings. FDA uses this authority to consult with external experts and to solicit their participation in advisory committee meetings as needed. FDA also communicates with relevant patient groups through our various patient listening sessions, patient and caregiver connection resource, and patient focused drug development meetings.

In addition, FDA convenes rare disease stakeholders in public meetings to hear different perspectives, on common issues in development of medical products across the spectrum of rare diseases. Recognizing these existing structures and mechanisms to facilitate rare disease product development, FDA agrees that there is value in external input on rare disease product development considerations, including through advisory committee meetings and other for a (e.g., workshops) and will continue to optimize strategies to leverage and obtain diverse expertise in the science and challenges of working with small populations.

When needed for rare diseases for which there is relevant expertise across the Agency, the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER) regularly consult the review staff in other centers. Beside the many available cross-Agency training and information sharing opportunities about rare diseases, extensive online medical information resources are available to FDA review staff through FDA's library for obtaining the most up-to-date medical literature about specific rare diseases.

Question 2. Has the review division consulted with patients about any safety signals or the benefit-risk assessment it is making before removing the accelerated approval pathway from consideration?

Answer 2. FDA recognizes the importance of the patient perspective to inform drug development and regulatory decisionmaking, regardless of the approval pathway utilized.

The Agency uses a variety of mechanisms to obtain the patient and caregiver perspective on safety issues and the balance of benefits and risks. Such mechanisms include patient listening sessions and patient focused drug development meetings, which are typically planned and held by or in collaboration with patient advocacy organizations, and public advisory committee meetings. Often, review staff hear first-hand from patients on their experiences in living with a specific rare disease during patient focused drug development meetings and listening sessions. During public advisory committee meetings, FDA solicits independent advice from external experts, which often includes patients, who provide their expertise on their condition to inform regulatory decisionmaking. Patient perspectives obtained from these different mechanisms often include the acceptability of certain risks given a drug's demonstrated benefits.

With respect to the accelerated approval pathway, accelerated approval requires a determination that the product has an effect on a surrogate endpoint—or an intermediate clinical endpoint—that is reasonably likely to predict clinical benefit. The assessment that a surrogate endpoint is reasonably likely to predict clinical benefit depends on the state of the science, including, for example, the depth of understanding of the pathogenesis of the disease. . The pathophysiology of some rare diseases remains incompletely understood, such that there may be considerable uncertainty in whether a drug's effect on a biomarker, for example, is reasonably likely to predict clinical benefit. Rare disease drug development is a dynamic and rapidly advancing field, so the optimal development pathway for a given product for a certain rare disease may evolve over time and we work closely with sponsors to consider the current state of science. The above mentioned patient and caregiver perspectives are carefully considered in decisions regarding accelerated approval of marketing applications.

Question 2. Beyond advancements in science, what are the most significant barriers that slow our ability to review applications for rare and ultra-rare therapies more expeditiously? Are there process or system improvements at the FDA that could enable the agency to further strengthen and accelerate its work reviewing therapies for these populations?

Answer 2. Development and review of rare disease applications frequently involve challenging considerations. For example, the natural history of a given rare disease may be poorly understood, there may be phenotypic and genotypic diversity within a disorder, drug development tools (e.g., outcome measures and biomarkers) often are lacking, and there may be a need to develop novel, clinically meaningful endpoints to facilitate drug development in many rare diseases.

These challenges necessitate a renewed focus on scientific research into rare diseases. Nevertheless, FDA remains committed to doing what it can to facilitate the review of proposed therapies for rare diseases. As an example, CDER recently launched the Accelerating Rare disease Cures (ARC) Program to harness our collective expertise and activities to provide strategic overview and coordination of the Center's rare disease activities. This program will

help address some of the common and significant barriers in rare disease product development. Although ARC is a CDER program, by strengthening CDER connections and collective vision it will enhance FDA's ability to continue work across the Agency. Enhancing these current partnerships and collaborations will broadly benefit rare disease product development.

Further, FDA's review of applications can be slowed when more information needs to be submitted by the applicant for FDA to continue its review and make a regulatory action. Although specific to each application, issues typically can be lumped under common topics or categories, such as certain aspects of manufacturing, product testing or safety data among many other topics. FDA continues to develop and issue guidance on a vast array of topics related to product development and application submission, including topics specific to rare diseases, to help applicants avoid pitfalls and submit the best possible applications to FDA for an expeditious review. FDA also provides outreach to stakeholders on such topics via presentations in various venues and on FDA webpages, all with the goal of improving the content and quality of submissions. Continued support of these outreach efforts will contribute to FDA's expeditious review of applications for new therapies including those for rare diseases.

> *Question 2(a)*. What approaches are there to help build FDA's knowledge on issues relevant to therapy development for rare and ultra-rare diseases, such as working with small populations and limited clinical trials data, and ensuring this knowledge can be applied agency-wide?

Answer 2. FDA's approach to building knowledge to facilitate the development of medical products for rare diseases, regardless of prevalence, is robust and collaborative, both across the Agency and with external stakeholders.

The Rare Diseases Team in CDER, Office of New Drugs (OND) coordinates with CBER, CDRH, and OOPD to collaborate on annual staff training to share learning and promote rare disease education regarding policy and review across the Agency. In addition, the Rare Diseases Team hosts quarterly seminars presented by internal and external experts to train and inform staff on timely and important aspects of rare disease drug development relevant to their work on rare disease applications. OND has also established a new Rare Disease Drug Development Council comprised of leaders from across CDER's OND and from CDER's Office of Translational Sciences with expertise and experience in rare disease drug development to promote organizational cohesion across rare disease issues and drug development programs. CBER and other Centers also participate in this new council. In spring 2022, CDER also launched the Accelerating Rare disease Cures (ARC) Program, which will drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases. ARC Program initiatives support the needs of CDER's drug review programs and associated CDER offices to foster scientific and regulatory innovation and engagement to enhance rare disease product development and advance rare disease regulatory science.

These types of approaches will further enhance collaboration, consistency, and knowledge sharing between OND divisions and across CDER and FDA, while ensuring that each rare disease drug development program is evaluated by staff that have the disease-specific expertise needed to appropriately design and evaluate these programs.

CBER's Rare Disease Program facilitates the Center's active participation in efforts with other rare disease partners across FDA to continue to build knowledge to advance development of therapies for rare diseases including those with very low prevalence. Collaborative activities include development and implementation of training for review staff, information sharing via stakeholder outreach and engagement activities (including patient engagement activities such as Patient Focused Drug Development meetings and Patient Listening Sessions), routine dialog with other regulatory authorities, guidance development, and FDA supported initiatives not specific to CBER. These activities focus on common issues and challenges faced in the development of medical products for rare diseases. CBER's Rare Disease Coordinating Committee, comprised of representatives from across the Center's Offices, provides a forum for information exchange on these efforts and rare disease related issues in general. CBER staff also participate and share information with other staff from across the agency in routine rare disease-related meetings such as the Rare Disease Council meetings led by OOPD and the Rare Disease Roundtable meetings led by CDER. CBER also collaborates with external stakeholders in efforts to address specific challenges encountered in development of CBER-regulated products such as cell and gene therapies and regenerative medicine therapies for rare diseases. Examples include partnering with NIH, joint public meetings with their National Center for Advancing Translational Science (NCATS), partnering with the Foundation for NIH, and working with others in establishing the Bespoke Gene Therapy Consortium to help advance development of gene therapies for rare diseases that affect one or a small number of individuals.

Question 3. How has patient engagement or patient-focused drug development supported innovation and what more can be done to ensure FDA is factoring the patient perspective into its regulatory activities?

Answer 3. Listening to the patients' perspectives through patient-focused drug development (PFDD) meetings or other venues supports identification of the benefits and risks that matter most to patients and helps identify new endpoints for innovative therapies.

Examples of CDER's ongoing efforts include the PFDD Meeting Program, conduct and participation in Patient Listening Sessions, conduct and participation in scientific round tables, and other activities that allow us to better understand the patient perspective. Additionally, the PFDD Guidance Series describes how stakeholders (patients, caregivers, researchers, medical product developers, and others) can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-

making. This guidance series has encouraged innovation by providing drug developers and patients with clarity on FDA's current thinking related to the quality of patient experience data that is submitted to FDA. Through programs such as the Standard Core Clinical Outcome Assessments and Related Endpoints Grant Program, CDER works cooperatively with grantees to develop core sets of clinical outcome assessments that include significant input from patients; several focus on rare diseases. This input is intended to help ensure that the endpoints being measured in clinical trials are endpoints that are meaningful to patients. When development is complete, CDER expects that these core sets will be made publicly available to medical product developers and others, potentially obviating the need for them to develop measures of their own. In addition, as part of our ongoing effort to ensure that CDER is factoring the patient perspective into our regulatory activities, under PDUFA VII we will be conducting internal trainings on patient-focused methodologies at least twice annually, and will issue a guidance document that focuses on patient preference studies.

The Centers also interact with patient groups on Center-specific topics and actively engage in Agency programs, initiatives, and events to gather patient input and share best practices for involving patients in medical product development and regulation. Patient engagement staff across the Agency including staff in the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Office of the Commissioner, work closely with staff from other FDA offices and programs, to coordinate patient engagement activities and patient-focused medical product development efforts, and to share best practices.

Examples of CBER efforts that support advancement of patient engagement and patient-focused medical product development include the Center's Science of Patient Input (SPI) initiative, its Rare Disease program, and patient-focused outreach on regenerative medicine product development. SPI initiative activities include supporting studies on methods and tools to obtain robust patient input to support biological product regulatory reviews and providing CBER reviewers with assistance in the regulatory review of patient input and patient-reported outcomes data. CBER's Rare Disease program works to facilitate the incorporation of the patient perspective into regulatory decision making for biologics for rare diseases. CBER's recent outreach efforts to facilitate patient engagement in development of regenerative medicine products, many of which are for rare diseases, include two public workshops for patient advocates (5/6/2021 and 5/24/2022) and the educational webinar series, RegenMedEd, which launched in November 2021 for patients, caregivers, and other stakeholders.

FDA also notes that CDRH has a robust Patient Science and Engagement Program that is committed to engaging with patients, understanding their experiences, and proactively integrating patient perspectives into medical device decisions and regulatory activities where appropriate. The Center has created forward-leaning mechanisms to facilitate patient involvement in regulatory activi-

ties as well as fostered innovative approaches to supporting the science of patient input. By collaborating with patients, healthcare providers, the research community, and industry, CDRH has fostered the creation of well-defined outcome measures and structured assessments of patient preferences that directly impact medical device decisions and assure that these devices include the evidence patients and providers depend upon rare disease regulatory science.

CDRH at the forefront of describing ways that structured collection of patient preference information can be used as scientific evidence in the evaluation of medical products. Since CDRH issued guidance on patient preference information in 2016, industry has been increasingly including this information in medical device submissions, growing from initially none to 26 studies that are completed or in the pipeline. In addition, patient-reported outcomes are being collected consistently in more than 50 percent of medical device submissions with clinical studies.[2] To better work hand-in-hand with patients to incorporate their values and perspectives into all aspects of the medical device total product life cycle, CDRH established the first advisory committee comprised solely of patients, caregivers and representatives of patient organizations called the Patient Engagement Advisory Committee (PEAC). The PEAC provides formal recommendations to FDA on general scientific matters related to medical devices such as patient involvement in the design and conduct of clinical trials, communicating cybersecurity vulnerabilities and medical device recalls, as well as the ways in which patient-generated health data can provide insights on medical device performance in real-world use. CDRH integrates the PEAC recommendations into regulatory actions like the recently issued final guidance[3] on the ways patients can engage as advisors in the design and conduct of clinical studies.

Question 4. Dr. Cavazzoni—According to cancer researchers, there is no one novel therapy that will be the magic bullet to cure all cancer patients. Many children and adults with cancer will need combinations of cancer therapies to achieve cures. However, unlike adults, childhood cancer provides little market incentive to develop new therapies because of its small population. As a result, current treatments for children are largely based on adult indications.

> *Question 4(a)*. What are some of the challenges the FDA faces as it tries to encourage companies to make combination therapies for children?

Answer 1. Section 504 of the FDA Reauthorization Act of 2017 (FDARA) amended section 505B of the FD&C Act to require—for original applications submitted on or after August 18, 2020—pediatric investigations of certain targeted cancer drugs with new active ingredients, based on molecular mechanism of action rather than clinical indication. Specifically, if an original new drug application (NDA) or biologics license application (BLA) is for a new active ingredient, and the drug that is the subject of the application is intended for treatment of an adult cancer and directed at a mo-

[2] *https://jpro.springeropen.com/articles/10.1186/s41687—022—00444—z*
[3] *https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/webinar—patient—engagement—design—and—conduct—medical—device—clinical—studies—final—guidance*

lecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer investigation (required under section 505B(a)(3) of the FD&C Act) must be submitted with the marketing application, unless FDA waives or defers the requirement. Importantly, this requirement applies to an original NDA or BLA for a new active ingredient for use in an oncology drug combination regimen with a previously approved product (provided that the other criteria in section 505B(a)(1)(B) of the FD&C Act are satisfied). FDARA thus created a mechanism to require evaluation of certain novel drugs that may have the potential to address an unmet medical need in the pediatric population, specifically, in pediatric cancer patients. FDA has fully implemented the FDARA amendments to section 505B of the FD&C Act, which has resulted in substantially increased numbers of timely pediatric investigations of novel cancer drugs potentially applicable to the treatment of children based on the molecular mechanism of action and the specific molecular targets to which the drugs are directed. Early evidence of activity also can support earlier incorporation of these novel agents into known effective combinations to evaluate further improvements in outcome. In addition, recent, histology-agnostic approvals of cancer drugs for different types of cancer in both adults and children based on the specific molecular driver or cause of a particular cancer predicts that the requirement for early pediatric investigation based on the molecular mechanism of action of a new drug, rather than indication, may result in approval for use of drugs for specific pediatric cancers, distinct from those adult cancers.

Despite these advancements, however, FDA does lack explicit authority to require study of combination drug regimens to treat cancer (including pediatric cancers) unless an application for such combination regimen has been submitted consistent with section 505B(a)(1) of the FD&C Act. There also is currently no statutory requirement for pre-clinical investigation of novel combinations of drugs in pediatric-specific tumor models to provide the evidence base to support clinical investigation of combinations in the pediatric population.

Question 5. There have been recent incidents where FDA has failed to meet agreed upon PDUFA dates with little justification or information given as to when a decision should be expected. This backlog is concerning as therapies are delayed from coming to market and patients are delayed access to new treatments that they have been eagerly waiting for. It is important for the FDA to prioritize meeting these timelines to ensure innovation and improved health outcomes for patients are not jeopardized.

> *Question 5(a)*. What is causing these delays that prevent the FDA from meeting these agreed upon product review deadlines and what is being done to clear the current backlog?

Answer 5. Since March 2020 when inspections were first impacted, FDA has generally continued to meet PDUFA user fee goal dates and has acted upon 90 percent or more of PDUFA applications each quarter throughout the pandemic. Delays in application

performance goals may occur for multiple reasons. Some examples include when there are deficiencies that must be corrected before an application can be approved, or where logistical challenges prevent FDA from conducting or completing necessary activities. An example of these latter logistical challenges brought on, or exacerbated by the pandemic, is traveling and safely conducting inspections, including in geographic locations where travel is restricted or limited.

During the pandemic, we increased our communication with sponsors and informed them if there was a need for inspection, if we expected to encounter delays in completing the inspection, and if we may not be able to complete the application review by the PDUFA goal date. Please see FDA's guidance for industry, *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID–19 Public Health Emergency Questions and Answers*.[4]

While continuing to conduct mission-critical and prioritized inspections, due to practical constraints, such as travel limitations, quarantine and social distancing requirements or lockdowns, we have increasingly relied on alternative approaches to inspections, including:

- Reviewing the inspection history of facilities to assess feasibility of relying on records or trusted partner inspections
- Using information shared by trusted foreign regulatory partners
- Requesting records directly from facilities in lieu of drug and biological product inspections
- Performing remote interactive evaluations in which we remotely evaluate live streamed video of facility operations and engage in other remote, live interactions with facility operators

FDA has found that, historically, only around 20 percent of applications warrant a pre-approval inspection (PAI) or pre-license inspection (PLI). FDA has used these alternative approaches to further reduce the need for PAIs/PLIs.

Where alternate tools are not available, insufficient, or otherwise will not satisfy the need for an inspection, FDA will use a risk-based approach to prioritize inspections, which includes consideration for (a) how product availability could impact public health; (b) investigator safety; and (c) travel restrictions or advisories associated with the location of the facility or site (e.g., country or region/state/province within the country, U.S. state, county, or territory).

As reported in the Resiliency Roadmap and the Roadmap Update,[5] between March 2020 and September 30, 2021, of the thousands of applications and supplements submitted, decisions on only 60 submissions were delayed solely due to a pending inspection that was postponed during the pandemic. Submissions under the PDUFA review program accounted for 35 of the delayed actions, but only 7 of these were for new drug applications The remaining

[4] *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-supply chain-and-drug-and-biological-product-inspections-during-covid–19-public-health*

[5] *https://www.fda.gov/media/154293/download*.

were for supplements to already approved drug applications. Since September 30, 2021, 10 additional submissions had a delayed action due to inspections, only 3 of which were new drugs. It is important to note that to date, we have not denied, and do not intend to deny, approval of a product application solely because we have been unable to complete a pre-approval inspection of a manufacturing facility or clinical trial site due to the COVID–19 pandemic.

With respect to new drug applications pending action due to inspections, all delayed mission critical submissions have now been acted upon.

Question 6. We know that certain ethnic and racial populations are underrepresented in biomedical research yet have a disproportionate disease burden for certain diseases. Recently, FDA released guidance titled: "Diversity Plans to Improve Enrollment of participants from Underrepresented Racial and Ethnic Populations in Clinical Trials."

> *Question 6(a)*. Can you describe the Agency's strategy to address diversity in clinical trials beyond this guidance and how the Agency will engage patient groups representative of ethnic and racial populations currently underrepresented?

Answer 6. FDA is committed to encouraging diverse participation in research used to support marketing applications for regulated medical products and has made progress in this area over the years. Physicians' ability to extrapolate results from clinical investigations to their own patients is dramatically improved when the participants in a clinical investigation reflect the product's intended patient population as closely as possible.

FDA is currently engaging in significant policy work relating to diversity in clinical investigations. We view modernizing clinical investigation design, conduct, and use of innovative technologies as ways to: enhance enrollment of diverse populations; facilitate the development of drugs, biological products, and devices; and improve efficiencies.

FDA has numerous efforts underway to encourage sponsors to increase the diversity of research participants in clinical investigations. These efforts are designed to help ensure that participants in clinical investigations reflect the population that ultimately may use the approved medical product. For example, FDA issued final guidance in November 2020, titled *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs*. The publication of this guidance followed a congressionally mandated public meeting on eligibility criteria that was held in April 2018 to help inform the content of the guidance. FDA also held Patient Engagement Advisory Committee (PEAC) meetings in 2017 and 2018 which focused on ways to engage diverse patients in the design and conduct of medical device clinical investigations. Based on the discussions held during both PEAC meetings and with consideration of comments submitted to a public docket, FDA issued final guidance in January 2022, titles *Patient Engagement in the Design and Conduct of Medical Device Clinical Studies*.

FDA's Office of Women's Health (OWH) conducts outreach on this important topic through the Diverse Women in Clinical Trials (DWCT) Initiative. This campaign was developed in collaboration with the NIH Office of Research on Women's Health to raise awareness about clinical investigation participation among women of different ages, races, ethnic backgrounds, disabilities, chronic illnesses, and health conditions. FDA's Office of Minority Health and Health Equity developed a Diversity in Clinical Trials Initiative which includes an ongoing, multi-media, public education and outreach campaign to help address some of the barriers preventing diverse groups from participating in clinical investigations through a variety of culturally and linguistically tailored strategies, tools, and resources, such as educational materials in multiple languages, a dedicated webpage with public service announcements and videos, social media outreach, and ongoing stakeholder engagement. FDA's Oncology Center of Excellence (OCE) has an active program to help improve diversity in clinical trials. Project Equity is a public health initiative established by OCE to ensure that the data submitted to FDA for approval of oncology medical products adequately reflects the demographic representation of patients for whom the medical products are intended. Project Equity works to improve access to clinical trials of oncology medical products for populations that have historically been underrepresented in clinical research such as racial and ethnic minorities, individuals who live in rural areas, sexual and gender minorities, and individuals with economic, linguistic, or cultural barriers to healthcare services.

FDA has ongoing efforts to promote the use of technology and innovative trial designs, such as decentralized investigations that bring the investigation to the participant's location, which may address some of these barriers. Decentralizing clinical trial activities may include the use of telehealth so patients can participate in trial visits from their homes. Direct distribution of medical products to patients' homes and the use of local clinical facilities near where patients live are other approaches to reduce the burden of trial participation. This can improve diversity of trial participants by reducing the time and expense of missing work, avoiding the need to arrange childcare, and eliminating the costs of travel, all which significantly impact minorities with less socio-economic resources. Additionally, FDA has published guidance encouraging sponsors to avoid excessively restrictive eligibility criteria which can be an additional barrier to clinical investigation participation.

Question 7. Given the impact of the COVID–19 pandemic on these patient groups, can you share any lessons learned from the pandemic that could be leveraged to improve clinical trial diversity?

Although progress has been made to increase the enrollment of diverse populations, there is still significant room for improvement. The current public health emergency further catalyzed FDA's efforts in this space. One strategy that needs to be scaled up in a sustainable way is engaging community clinicians in the clinical trial research efforts. There is considerable evidence that clinician

recommendations play an important role in helping patients to consider participating in clinical investigations. [6]

The COVID–19 pandemic has highlighted the ability of technology to enable remote assessment of safety and efficacy outcomes in clinical trials. Such technology allows decentralized investigations that bring the investigation to the participant's location, thus decreasing the financial and time or logistical burden of clinical trial participation. Therefore, more patients with fewer resources may be able to participate in clinical trials and improve the diversity of the study populations.

SENATOR TUBERVILLE

Question 1. The User Fee Agreements are a big deal here in DC. They represent the product of years of discussion and negotiation between the FDA, industry, and other stakeholders. But, most regular Americans do not pay attention to these negotiations. I hear from my constituents all the time about rising prescription drug costs, but no one ever mentions the FDA User Fee agreements. How would you explain to my constituents back home how these new agreements are going to help them?

Answer 1. The User Fee agreements provide FDA with necessary resources, establish priorities and review structure, and foster new and innovative programs which facilitate development and approval of medical products. For example, FDA has seen a sustained increase in development program activities, including investigational new drug applications and formal meeting requests. A number of these development programs have the potential to bring new therapies to meet unmet medical needs for serious and life-threatening diseases.

Generally, the User Fee agreements will allow the Agency to produce multiple guidances; host public meetings to examine new technologies and approaches; host patient-focused drug development meetings to better understand patient perspectives on gene therapy products; and conduct public outreach to facilitate product development and approval.

Below are specifics for each program:

- PDUFA—Now in its seventh authorization, PDUFA has proven to be an extremely effective program that has transformed U.S. drug review process to the fastest in the world, while setting the global gold standard for quality, efficacy, and safety. As reflected in the PDUFA commitment letter, PDUFA VII, when enacted, will also provide for additional resources for the cell and gene therapy program. New allergenic extract products are also included in PDUFA VII, and the program will provide needed resources to facilitate the timely development and approval of new medical products critical for the diagnosis and treatment of allergies, including serious food allergies.
- GDUFA—Now in its third authorization, GDUFA aims to put FDA's generic drug program on a firm financial

[6] *https://www.nejm.org/doi/full/10.1056/NEJMp2107331*

footing and ensure timely access to safe, high-quality, affordable generic drugs. GDUFA enables FDA to assess user fees to fund critical and measurable enhancements to the performance of FDA's generic drugs program, bringing greater predictability and timeliness to the review of generic drug applications.

- BsUFA—Now in its third authorization, BsUFA aims to expedite the review process for biosimilar biological products. Biosimilar biological products represent an important public health benefit, with the potential to offer life-saving or life-altering benefits at reduced cost to the patient. BsUFA facilitates the development of safe and effective biosimilar products for the American public.
- MDUFA—Now in its fifth authorization, MDUFA has enabled patients to have timely access to more innovative and better performing devices—and therefore more options—than at any other time in our history. MDUFA supports FDA's capacity to assess new medical device technologies, provides a predictable, transparent path to market, and upholds FDA's rigorous review standards. MDUFA also promotes accountability for the Center's performance and operations, and makes critical investments in the future of the program, to assure FDA has the resources to handle review of the robust pipeline of new technology and the innovations of tomorrow.

Question 2. I hear from constituents who are concerned about the FDA's draft guidance on homeopathic products. The guidance takes a different position than the FDA has historically taken on the regulation of homeopathic medicines. Since inclusion in the Food, Drug, and Cosmetic Act of 1938, homeopathic medicines have been recognized as a unique and separate category of drugs. The FDA stated in the past that "the law gives the FDA no premarket review of true homeopathic dilutions." Yet, the draft guidance takes a new position deeming all homeopathic products as unapproved new drugs subject to pharmaceutical-specific premarket approval.

Question 2(a). Is FDA is seeking a revised regulatory framework with regard to homeopathic medicines?

Question 2(b). If so, how does the Agency's reinterpretation of longstanding law and corresponding regulations and policies fall within the purview of guidance documents?

Answer 2. FDA appreciates the opportunity to clarify the Agency's approach to its regulation of homeopathic drug products.

We first note that as described in the Agency's October 2019 revised draft Guidance, *Drug Products Labeled as Homeopathic,*[7] the definition of "drug" in section 201(g)(1) of the FD&C Act, 21 U.S.C. 321(g)(1), includes articles recognized in the Homeopathic Pharmacopeia of the United States. As such, homeopathic drugs are subject to the same statutory requirements as other drugs; nothing in the FD&C Act exempts homeopathic drug products from any of the re-

[7] *https://www.fda.gov/media/131978/download*

quirements related to approval, adulteration, or misbranding, including labeling requirements.

There are currently no homeopathic drug products that are approved by FDA. Products labeled as homeopathic and currently marketed in the U.S. have not been reviewed by the FDA for safety and effectiveness to diagnose, treat, cure, prevent or mitigate any diseases or conditions.

On October 24, 2019, FDA withdrew Compliance Policy Guide (CPG) 400.400, entitled "Conditions Under Which Homeopathic Drugs May be Marketed," because it was inconsistent with our risk-based approach to regulatory and enforcement action. FDA also issued the revised draft guidance: Drug Products Labeled as Homeopathic, for public comment. This revised draft guidance proposes a comprehensive, risk-based enforcement approach to homeopathic products marketed without FDA approval. When finalized, this guidance will help provide transparency regarding the categories of homeopathic drug products that we intend to prioritize under our risk-based enforcement approach. In the meantime, FDA is applying its general approach to prioritizing regulatory and enforcement action, which involves risk-based prioritization considering all the relevant facts of a given situation. We note that the draft guidance, when finalized, would not represent a change in the legal obligations that currently apply to homeopathic drugs under the statutes FDA administers.

FDA sought broad public input as the Agency evaluated its enforcement policies for homeopathic products to better promote and protect the public health.[8] Our top concern is patient safety.

FDA is currently working to finalize the revised draft guidance on homeopathic drug products and has reviewed comments submitted to the docket. You can review these comments online at: *https://www.regulations.gov/document/FDA–2017-D—6580—4828/comment* (Docket No. FDA–2017-D–6580). When finalized, this guidance will represent the Agency's current thinking. The Agency is unable to comment at this time on the pending content of the final guidance. When it is posted and the Notice of Availability publishes in the Federal Register, we will be able to publicly discuss the contents.

Question 3. Legislation and policy ideas around improving the Accelerated Approval pathway are focused on what sponsors can do better with respect to confirmatory trials. However, I am also concerned that, aside from oncology, FDA hasn't been using this pathway as actively as it could be in rare diseases. I'm also concerned that not all review divisions understand or apply the accelerated pathway appropriately.

> *Question 3(a)*. How is FDA ensuring that expertise about the use of the accelerated approval pathway is being shared within the Agency's divisions?

[8] April 2015, FDA held a public hearing to obtain information and comments from stakeholders about the current use of homeopathic drug products, as well as the Agency's regulatory framework for such products (Docket No. FDA–2015-N–0540; available at *https://www.regulations.gov/docket/FDA–2015-N–0540)*. In October 2019, FDA issued revised draft guidance ("Drug Products Labeled as Homeopathic"), as noted above, in response to public comments received on the initial December 2017 draft version.

Answer 3. We recognize that collaboration and information sharing are important aspects of facilitating rare disease product development. This collaboration and information sharing occurs with external stakeholders and within FDA. In terms of internal collaboration, we are committed to information sharing, both through formal and informal mechanisms.

For example, we routinely share information and discuss challenging issues in rare disease product development across review divisions through multiple mechanisms. FDA has several widely attended internal forums for discussion, including CDER's Medical Policy and Program Review Council and the Rare Disease Drug Development Council (RDDDC), with the latter being dedicated to discussing development programs for rare diseases. The RDDDC facilitates not only cross-division discussion and sharing of expertise, which could include topics such as the use of accelerated approval, but also invites staff from other Centers to participate as well. Both of these councils include leaders across the Office of New Drugs and the Office of Translational Sciences, which helps bring cross-disciplinary, senior Agency expertise to advise review divisions regarding challenging issues that arise in drug development. As another example of information sharing, important regulatory decisions on rare disease marketing applications are shared by rare disease staff through internal communications in both CDER and CBER.

Further, to ensure expertise about the use of the accelerated approval pathway is shared, training on expedited programs including accelerated approval is provided to FDA review staff on a regular basis and is available in recorded format for review at any time.

> *Question 3(b)*. How is FDA using external expertise to appropriately make risk-benefit decisions for rare and ultra-rare diseases when safety is established, there are no other treatment options, and the condition is life threatening or significantly impacting quality of life?

Answer 3(b). FDA recognizes that there is significant unmet need for patients and families living with rare diseases as most rare diseases do not have approved therapies at this time. As further discussed below, these circumstances are considered and incorporated into FDA's approach to rare diseases, regardless of the regulatory pathway used or available for a particular development program.

It is important to understand that FDA considers safety and clinical benefit in its review and this benefit-risk assessment takes into account the seriousness of the disease. Benefit-risk assessment is integrated into FDA's regulatory review of marketing applications. The benefit-risk assessment includes many factors, such as the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be needed. As articulated in our 2019 draft guidance that addresses dem-

onstrating substantial evidence of effectiveness,[9] FDA recognizes that some patients and their caregivers are willing to accept less certainty about effectiveness in return for earlier access to much needed medicines. For example, for a life-threatening disease without any available treatment, FDA might accept the results of adequate and well-controlled investigations with less rigorous designs, such as historically controlled studies. FDA has approved many drugs for rare diseases by applying these principles, using both traditional and accelerated approval pathways, when there is evidence that the drug is effective. Importantly, rare disease drug development spans therapeutic areas. FDA has mechanisms and initiatives, such as policy councils and the Rare Diseases Team, to facilitate consistency across divisions around rare disease product development considerations, such as the use of accelerated approval and considerations related to regulatory flexibility.

FDA's clinical review staff take advantage of a multitude of resources to gain knowledge on rare diseases when the agency determines such advice would be helpful as FDA considers the risks and benefits of medical products, including those intended for rare diseases based on the statutory definition (i.e., <200,000 in the U.S.).

Development and review of rare disease applications frequently involves challenging considerations that may benefit from discussion with external experts, such as at advisory committee meetings. FDA uses this authority to consult with external experts and to solicit their participation in advisory committee meetings as needed. FDA also communicates with relevant patient groups through our various patient listening sessions, patient and caregiver connection resource, and patient focused drug development meetings.

In addition, FDA convenes rare disease stakeholders in public meetings to hear different perspectives, on common issues in development of medical products across the spectrum of rare diseases. Recognizing these existing structures and mechanisms to facilitate rare disease product development, FDA agrees that there is value in external input on rare disease product development considerations, including through advisory committee meetings and other for a (e.g., workshops) and will continue to optimize strategies to leverage and obtain diverse expertise in the science and challenges of working with small populations.

When needed for rare diseases for which there is relevant expertise across the Agency, the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER) regularly consult the review staff in other centers. Beside the many available cross-Agency training and information sharing opportunities about rare diseases, extensive online medical information resources are available to FDA review staff through FDA's library for obtaining the most up-to-date medical literature about specific rare diseases.

Question 3(c). What is FDA's oversight of its own divisions, especially when departing from earlier openness to a path-

[9] *https://www.fda.gov/media/133660/download*. When finalized, this will represent FDA's current thinking on this issue.

way that would promise much earlier access to treatments where patients lack any other treatments?

Answer 3(c). Use of the accelerated approval pathway requires a determination that the product has an effect on a surrogate endpoint—or an intermediate clinical endpoint—that is reasonably likely to predict clinical benefit. The assessment that a surrogate endpoint is reasonably likely to predict clinical benefit reflects a scientific decision based on numerous considerations, including the depth of understanding of the pathogenesis of the disease. Unfortunately, many diseases, including many rare diseases, are poorly understood, which may complicate assessment of proposed surrogate endpoints. FDA has several forums and mechanisms for considering these scientific issues, such as policy councils, including the Medical Policy and Program Review Council and the Rare Disease Drug Development Council.

In addition, FDA is committed to having meetings with sponsors to discuss challenging product development issues. For example, product developers can request Type C meetings to discuss surrogate endpoints. Such meetings will allow FDA to engage with sponsors who would like to employ a biomarker as a surrogate endpoint that has not been used previously as the primary basis for product approval in the proposed context of use. Sponsors who request these meetings may benefit from a discussion about whether a surrogate endpoint could support a traditional or accelerated approval. The meetings also allow for early identification of any gaps in scientific knowledge (e.g., of the disease being treated) and discussion of how they might be addressed. Early consultation in the drug development program allows the review team to consult with FDA leadership and subject matter experts, as necessary, to evaluate the sponsor's proposal before providing advice regarding the proposed surrogate endpoint to support accelerated or traditional approval. In addition, product developers are encouraged to consult with FDA should new information become available that could affect the assessment of the likelihood that a surrogate endpoint predicts clinical benefit (either positively or negatively).

Question 3(d). How does FDA evaluate its own review divisions' decisions to withdraw the accelerated pathway in a way that is applied uniformly across divisions or is defensible?

Answer 3(d). The process and grounds for withdrawal of approval of a product or indication approved under accelerated approval are well defined in statute (Section 506(c) of the FD&C Act), FDA regulations (21 CFR 601.43 and 314.530), and the Expedited Programs Guidance. The process includes written notification to the applicant for an opportunity for a hearing, a Federal Register notice of the hearing, and an advisory committee constituted under 21 CFR part 14.

FDA has a number of mechanisms to discuss and evaluate scientific considerations, including those related to whether the accelerated approval pathway is appropriate for a given drug development program.

For example, although there are currently 27 clinical review divisions in CDER's Office of New Drugs, these divisions report to only eight clinical offices that align interrelated disease areas. Thus, office leadership is well-positioned to facilitate the sharing of knowledge and experience between review divisions. Input of other leaders is often sought, however, especially for challenging issues in drug development. CDER has several councils that may discuss and advise review divisions on scientific and regulatory considerations, such as the Medical Policy and Program Review Council and the Rare Disease Drug Development Council. CDER also has a Rare Diseases Team that facilitates, supports, and accelerates the development of drugs and therapeutic biologics for rare diseases. This includes providing advice to review divisions on their rare disease programs as requested and promoting rare disease considerations across CDER's Office of New Drugs. Similarly, CBER's products are organized into three product offices. Their leadership facilitates knowledge sharing and experience within their Offices and across the Center. Within CBER, Councils have been established where challenging scientific and clinical issues can be discussed. CBER also participates in many CDER Councils and groups and Centers may also consult each other on specific issues.

RESPONSE BY PETER MARKS TO QUESTIONS FROM SENATOR CASEY, SENATOR COLLINS, SENATOR CASSIDY, SENATOR SCOTT, AND SENATOR TUBERVILLE

SENATOR CASEY

Pennsylvania is home to a thriving life sciences industry pioneering promising new fields of medicine. I have been particularly excited to hear about tremendous progress in the area of cell and gene therapy and the promise they hold in curing devastating diseases and transforming the lives of patients. Since many of these advanced therapies are cutting-edge and hold the potential to address unmet medical needs, my understanding is that these companies are often entitled to pre-application meetings with the FDA. In setting up these expedited programs and authorizing previous PDUFA agreements, Congress intended for these meetings to help facilitate their applications and streamline the review process, ultimately delivering treatments that prove safe and effective to patients as quickly as possible.

I have heard from companies working on next-generation therapies that the FDA frequently responds to their meeting requests with so-called "written response only" (WRO). Understandably, these written responses do not allow the same opportunities for exchanges and context that make the meetings as useful as possible to both parties. I am concerned that progress on these technologies could be slowed by insufficient face-to-face communication—the intention for these meetings—and an overreliance on WROs.

Question 1. Why have WROs become so common in responding to meeting requests? Is CBER able to meet the demands of these congressionally mandated programs with its current resources and staff?

Answer 1. Written response only (WRO) is one of three formats for formal meetings with FDA (see: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry)*. WROs are an important and efficient tool to respond to drug developer questions that only require straightforward responses, questions that are already addressed in published FDA guidance, or other questions that can be readily addressed in writing. CBER has experienced increased workload especially in the areas of Cellular and Gene Therapies which is regulated by the Office of Tissues and Advanced Therapies (OTAT). OTAT currently has over 3,000 active Investigational New Drug Applications (INDs). Over the past 5 years, there has been a rapid increase in the number of meeting requests, with a related rapid increase in the number of meetings granted, exceeding the rate of increase in OTAT review staff. OTAT has seen a sustained increase in development program activities, including an 85 percent increase in INDs, and a 158 percent increase in formal meeting requests. Thus, OTAT does not currently have the manpower to hold face-to-face communications for every meeting request for a face-to-face meeting and must be selective in order to be most efficient with available resources. Meetings, while important, are only one aspect of developing innovative products to address unmet medical needs and resources must be applied to other areas (e.g., review, guidance).

> *Question 1(a)*. How does the FDA determine which meeting requests receive live engagements and which are relegated to WROs?

Answer 1(a). For each meeting request, CBER carefully considers the specific questions posed by the drug developer, as well as the context (e.g., stage of development, product complexity, clinical indication and unmet need). Considerations include whether the questions and associated responses are straight-forward or nuanced and complex, can be easily addressed in writing, are already addressed in our published guidance documents, or have been previously discussed with the drug developer. If we expect that our responses will be straight-forward (e.g., referral to content of a specific guidance document) or will reiterate points made in previous discussions with the sponsor, then we are more likely to provide written responses. If the questions are complex, with a product that raises new scientific questions, or an innovative trial design, we are more likely to communicate on a telecon. In addition, CBER prioritizes meeting requests for products that have Breakthrough Therapy Designation or Regenerative Medicine Advanced Therapy (RMAT) Designation.

> *Question 1(b)*. What steps does the FDA take to ensure that programs which address the most pressing unmet medical needs receive prioritized attention to ensure their review is not unnecessarily delayed?

Answer 1(b). Fast Track designation and Breakthrough Therapy designation are expedited drug development and review programs that provide sponsors with prioritized attention through earlier and

more frequent interactions with FDA for drug development programs that meet certain criteria. In addition, biological products identified as regenerative medicine therapies and intended to address an unmet medical need may be eligible for Regenerative Medicine Advanced Therapy (RMAT) designation, an expedited development program established under the 21st Century Cures Act that provides similar and additional benefits. A drug development program granted designation under any one of these three programs, may be eligible for priority review designation and a rolling review, each of which may help speed review. Sponsors submit a separate request for each of these programs and may be granted designation for more than one program. FDA guidance on these programs is available. (See Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Guidance for Industry at https://*www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions and Expedited Programs for Serious Conditions—Drugs and Biologics at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics).*

SENATOR COLLINS

Question 1. CBER will receive significant new resources under the new agreement in exchange for meeting specific performance goals, including improvements to how the Center engages with sponsors. The commitment letter gives FDA discretion to choose the format of necessary meetings between the agency and drug sponsors, but I have heard serious concerns that FDA is responding to some meeting requests with a "written response only."

The written response counts as a meeting for purposes of tracking whether FDA is upholding its commitments, but it is actually effectively declining a meeting, because the written response ends the interaction. There is no opportunity for dialog on key issues, which can result in miscommunications that delay research and the development process—and can have a negative impact for patients involved in clinical trials.

This is particularly problematic in the cell and gene therapy space, which may promise cures to vexing diseases like Type 1 diabetes and Duchenne Muscular Dystrophy, but also introduces new questions for regulatory science. How does CBER plan to improve the quality of interaction with sponsors given the new resources provided under the agreement?

Answer 1. Sponsors will have access to additional engagement and communication with FDA's expert scientific staff via some of the enhancements under PDUFA VII, once it is enacted. The PDUFA VII commitment letter includes a new Type D meeting, INTERACT meeting, and a follow-up opportunity following sponsor meetings to confirm understanding of the communications that took place. Similar enhancements with respect to biosimilar and interchangeable biological products are described in the BsUFA III commitment letter. For example, the BsUFA III commitment letter includes a new Type 2a meeting, increased flexibility in requesting

Biosimilar Initial Advisory meetings, and the same post-meeting follow-up opportunity as in PDUFA.

SENATOR CASSIDY

Question 1. In recent months, FDA has issued more Complete Response Letters (CRLs) than approvals of applications for drugs to treat patients with chronic kidney disease [including CRLs on veverimer, taurolidine, tenapanor, roxadustat, bardoxolone and vadadustat]. How is FDA applying its benefit/risk framework to new drugs to treat this chronically ill patient population at high risk of serious cardiovascular and other complications, and working with drug developers to ensure there are clear rules of the road to demonstrate safety and efficacy?

Answer 1. Please see FDA response in CDER section above.

Question 2. Historically, the nephrology division at the FDA had one of the lowest rates of new drug applications submitted, particularly compared to oncology and cardiology. How does the FDA ensure that the legal standards are being applied equally by each division?

Answer 2. Please see FDA response in CDER section above.

Question 3. A pillar of the PDUFA VII commitment letter is greater communication between FDA and drug sponsors to ensure that drug development programs have clear metrics, including for safety and clinical end points. How will these new commitments reduce unexpected analyses or standards introduced late in the development or application process for therapies developed to treat patients with kidney disease?

Answer 3. Please see FDA response in CDER section above.

Question 4. Another pillar of the commitment letter is building on a focus of Patient Focused Drug Development to ensure that the patient voice in incorporated into drug development decision-making. How can we ensure that FDA takes into consideration patient preferences and potential acceptability of tradeoffs between treatment benefit and risk outcomes in high risk diseases like kidney disease?

Answer 4. Please see FDA response in CDER section above.

SENATOR SCOTT

Question 1. Patients have expressed concerns that not all review divisions within FDA understand or apply the accelerated pathway appropriately. Some have even likened the experience to that of a "lottery" as to whether they'll be assigned a division with experience in ultra-rare conditions with well under 20,000 patients in the U.S.—and oftentimes only 2,000 or even 200 patients. How is FDA using external expertise to appropriately make risk-benefit decisions for rare and ultra-rare diseases when safety is established, there are no other treatment options, and the condition is life threatening or significantly impacting quality of life?

> *Question 1(a)*. Has the review division consulted with patients about any safety signals or the benefit-risk assessment it is making before removing the accelerated approval pathway from consideration?

Answer 1. Please see FDA response in CDER section above.

Question 2. Beyond advancements in science, what are the most significant barriers that slow our ability to review applications for rare and ultra-rare therapies more expeditiously? Are there process or system improvements at the FDA that could enable the agency to further strengthen and accelerate its work reviewing therapies for these populations?

Question 2(a). What approaches are there to help build FDA's knowledge on issues relevant to therapy development for rare and ultra-rare diseases, such as working with small populations and limited clinical trials data, and ensuring this knowledge can be applied agency-wide?

Question 2(b). How has patient engagement or patient-focused drug development supported innovation and what more can be done to ensure FDA is factoring the patient perspective into its regulatory activities?

Answer 2. Please see FDA response in CDER section above.

Question 3. According to CBER's PDUFA performance metrics from October 2019 to present, despite the pandemic workload, CBER has largely been getting meeting summaries to sponsors on time (0–6 percent late per quarter). However, a lot of these summaries are written responses to the sponsor for meetings that were not held, leading to stakeholder concerns that this could mean CBER is focused more on checking the box for meetings with sponsors by using written responses only.

Question 3(a). With the large influx of resources—both people and money—for CBER under PDUFA VII—what is the industry's expectation regarding CBER's use of Written Response Only versus live meetings?

Answer 3. CBER will continue to use all available resources to communicate effectively with stakeholders. CBER will continue to carefully prioritize each meeting request with regard to written responses only versus live meetings, based on a variety of factors, including complexity of the question, whether the request involves new scientific questions, ability to answer the question in a written form or by referencing guidance, and changes in the workload relative to the availability of resources. If we expect that our responses will be straight-forward (e.g., referral to content of a specific guidance document) or will reiterate points made in previous discussions with the sponsor, then we are more likely to provide written responses. If the questions are complex, with a product that raises new scientific questions, or an innovative trial design, we are more likely to communicate on a telecon.

Of note, CBER is also planning to increase other forms of communication (e.g., webinars, guidances), which we believe will help decrease the need for individual sponsor meetings. Meetings with industry, while important, are only one aspect of developing innovative products (e.g., review, guidance) for which PDUFA resources are applied.

Question 4. There have been recent incidents where FDA has failed to meet agreed upon PDUFA dates with little justification or

information given as to when a decision should be expected. This backlog is concerning as therapies are delayed from coming to market and patients are delayed access to new treatments that they have been eagerly waiting for. It is important for the FDA to prioritize meeting these timelines to ensure innovation and improved health outcomes for patients are not jeopardized.

Question 4(a). What is causing these delays that prevent the FDA from meeting these agreed upon product review deadlines and what is being done to clear the current backlog?

Answer 4. Please see FDA response in CDER section above.

Question 5. We know that certain ethnic and racial populations are underrepresented in. Can you describe the Agency's strategy to address diversity in clinical trials beyond this guidance and how the Agency will engage patient groups representative of ethnic and racial populations currently underrepresented? biomedical research yet have a disproportionate disease burden for certain diseases. Recently, FDA released guidance titled: "Diversity Plans to Improve Enrollment of participants from Underrepresented Racial and Ethnic Populations in Clinical Trials." biomedical research yet have a disproportionate disease burden for certain diseases. Recently, FDA released guidance titled: "Diversity Plans to Improve Enrollment of participants from Underrepresented Racial and Ethnic Populations in Clinical Trials."

Answer 5. Please see FDA response in CDER section above.

SENATOR TUBERVILLE

Question 1. The User Fee Agreements are a big deal here in DC. They represent the product of years of discussion and negotiation between the FDA, industry, and other stakeholders. But, most regular Americans do not pay attention to these negotiations. I hear from my constituents all the time about rising prescription drug costs, but no one ever mentions the FDA User Fee agreements. How would you explain to my constituents back home how these new agreements are going to help them?

Answer 1. Please see FDA response in CDER section above.

Question 2. I hear from constituents who are concerned about the FDA's draft guidance on homeopathic products. The guidance takes a different position than the FDA has historically taken on the regulation of homeopathic medicines. Since inclusion in the Food, Drug, and Cosmetic Act of 1938, homeopathic medicines have been recognized as a unique and separate category of drugs. The FDA stated in the past that "the law gives the FDA no premarket review of true homeopathic dilutions." Yet, the draft guidance takes a new position deeming all homeopathic products as unapproved new drugs subject to pharmaceutical-specific premarket approval.

Question 2(a). Is FDA seeking a revised regulatory framework with regard to homeopathic medicines?

Question 2(b). If so, how does the Agency's reinterpretation of longstanding law and corresponding regulations and policies fall within the purview of guidance documents?

Answer 2. Please see FDA response in CDER section above.

Question 3. Legislation and policy ideas around improving the Accelerated Approval pathway are focused on what sponsors can do better with respect to confirmatory trials. However, I am also concerned that, aside from oncology, FDA hasn't been using this pathway as actively as it could be in rare diseases. I'm also concerned that not all review divisions understand or apply the accelerated pathway appropriately.

Question 3(a). How is FDA ensuring that expertise about the use of the accelerated approval pathway is being shared within the Agency's divisions?

Question 3(b). How is FDA using external expertise to appropriately make risk-benefit decisions for rare and ultra-rare diseases when safety is established, there are no other treatment options, and the condition is life threatening or significantly impacting quality of life?

Question 3(c). What is FDA's oversight of its own divisions, especially when departing from earlier openness to a pathway that would promise much earlier access to treatments where patients lack any other treatments?

Question 3(d). How does FDA evaluate its own review divisions' decisions to withdraw the accelerated pathway in a way that is applied uniformly across divisions or is defensible?

Answer 3. Please see FDA response in CDER section above.

RESPONSE BY JEFFREY SHUREN TO QUESTIONS FROM SENATOR SCOTT, AND SENATOR TUBERVILLE

SENATOR SCOTT

Question 1. Patients have expressed concerns that not all review divisions within FDA understand or apply the accelerated pathway appropriately. Some have even likened the experience to that of a "lottery" as to whether they'll be assigned a division with experience in ultra-rare conditions with well under 20,000 patients in the U.S.—and oftentimes only 2,000 or even 200 patients.

Question 1(a). How is FDA using external expertise to appropriately make risk-benefit decisions for rare and ultra-rare diseases when safety is established, there are no other treatment options, and the condition is life threatening or significantly impacting quality of life?

Question 1(b). Has the review division consulted with patients about any safety signals or the benefit-risk assessment it is making before removing the accelerated approval pathway from consideration?

Answer 1. Please see FDA response in CDER section above.

Question 2. Beyond advancements in science, what are the most significant barriers that slow our ability to review applications for rare and ultra-rare therapies more expeditiously? Are there process or system improvements at the FDA that could enable the agency

to further strengthen and accelerate its work reviewing therapies for these populations?

Question 2(a). What approaches are there to help build FDA's knowledge on issues relevant to therapy development for rare and ultra-rare diseases, such as working with small populations and limited clinical trials data, and ensuring this knowledge can be applied agency-wide?

Question 2(b). How has patient engagement or patient-focused drug development supported innovation and what more can be done to ensure FDA is factoring the patient perspective into its regulatory activities?

Answer 2. Please see FDA response in CDER section above.

Question 3. There have been recent incidents where FDA has failed to meet agreed upon PDUFA dates with little justification or information given as to when a decision should be expected. This backlog is concerning as therapies are delayed from coming to market and patients are delayed access to new treatments that they have been eagerly waiting for. It is important for the FDA to prioritize meeting these timelines to ensure innovation and improved health outcomes for patients are not jeopardized.

Question 3(a). What is causing these delays that prevent the FDA from meeting these agreed upon product review deadlines and what is being done to clear the current backlog?

Answer 3. Please see FDA response in CDER section above.

Question 4. We know that certain ethnic and racial populations are underrepresented in biomedical research yet have a disproportionate disease burden for certain diseases. Recently, FDA released guidance titled: "Diversity Plans to Improve Enrollment of participants from Underrepresented Racial and Ethnic Populations in Clinical Trials."

Question 4(a). Can you describe the Agency's strategy to address diversity in clinical trials beyond this guidance and how the Agency will engage patient groups representative of ethnic and racial populations currently underrepresented?

Question 4(b). Given the impact of the COVID–19 pandemic on these patient groups, can you share any lessons learned from the pandemic that could be leveraged to improve clinical trial diversity?

Answer 4. Please see FDA response in CDER section above.

SENATOR TUBERVILLE

Question 1. The User Fee Agreements are a big deal here in DC. They represent the product of years of discussion and negotiation between the FDA, industry, and other stakeholders. But, most regular Americans do not pay attention to these negotiations. I hear from my constituents all the time about rising prescription drug costs, but no one ever mentions the FDA User Fee agreements. How would you explain to my constituents back home how these new agreements are going to help them?

Answer 1. Please see FDA response in CDER section above.

Question 2. I hear from constituents who are concerned about the FDA's draft guidance on homeopathic products. The guidance takes a different position than the FDA has historically taken on the regulation of homeopathic medicines. Since inclusion in the Food, Drug, and Cosmetic Act of 1938, homeopathic medicines have been recognized as a unique and separate category of drugs. The FDA stated in the past that "the law gives the FDA no premarket review of true homeopathic dilutions." Yet, the draft guidance takes a new position deeming all homeopathic products as unapproved new drugs subject to pharmaceutical-specific premarket approval.

Question 2(a). Is FDA seeking a revised regulatory framework with regard to homeopathic medicines?

Question 2(b). If so, how does the Agency's reinterpretation of longstanding law and corresponding regulations and policies fall within the purview of guidance documents?

Answer 2. Please see FDA response in CDER section above.

Question 3. Legislation and policy ideas around improving the Accelerated Approval pathway are focused on what sponsors can do better with respect to confirmatory trials. However, I am also concerned that, aside from oncology, FDA hasn't been using this pathway as actively as it could be in rare diseases. I'm also concerned that not all review divisions understand or apply the accelerated pathway appropriately.

Question 3(a). How is FDA ensuring that expertise about the use of the accelerated approval pathway is being shared within the Agency's divisions?

Question 3(b). How is FDA using external expertise to appropriately make risk-benefit decisions for rare and ultra-rare diseases when safety is established, there are no other treatment options, and the condition is life threatening or significantly impacting quality of life?

Question 3(c). What is FDA's oversight of its own divisions, especially when departing from earlier openness to a pathway that would promise much earlier access to treatments where patients lack any other treatments?

Question 3(d). How does FDA evaluate its own review divisions' decisions to withdraw the accelerated pathway in a way that is applied uniformly across divisions or is defensible?

Answer 3. Please see FDA response in CDER section above.

[Whereupon, at 11:44 a.m., the hearing was adjourned.]

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