

**IMPLEMENTATION OF THE  
21ST CENTURY CURES ACT:  
PROGRESS AND THE PATH  
FORWARD FOR MEDICAL INNOVATION**

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**HEARING**  
OF THE  
**COMMITTEE ON HEALTH, EDUCATION,  
LABOR, AND PENSIONS**  
**UNITED STATES SENATE**  
**ONE HUNDRED FIFTEENTH CONGRESS**

FIRST SESSION

ON

EXAMINING IMPLEMENTATION OF THE 21ST CENTURY CURES ACT, FO-  
CUSING ON PROGRESS AND THE PATH FORWARD FOR MEDICAL IN-  
NOVATION

DECEMBER 7, 2017

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**Thursday, December 7, 2017**

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

The Committee met, pursuant to notice, at 10:10 a.m., in room SD-430, Dirksen Senate Office Building, Hon. Lamar Alexander, Chairman of the Committee, presiding.

Present: Senators Alexander [presiding], Collins, Cassidy, Young, Hatch, Roberts, Scott, Murray, Casey, Bennet, Whitehouse, Baldwin, Murphy, Warren, Kaine, and Hassan.

**OPENING STATEMENT OF SENATOR ALEXANDER**

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order.

This is another bipartisan hearing, which is what most of our hearings are, which means that Senator Murray and I have agreed on the subject and on the witnesses. In fact, I would say every Member of this Committee would probably agree on the subject and the witnesses today, because this is a hearing entitled “Implementation of the 21st Century Cures Act: Progress and the Path Forward for Medical Innovation” to hear from Dr. Francis Collins, the Director of the National Institutes of Health, and Dr. Scott Gottlieb, the Commissioner of Food and Drugs.

We’ll have—as I mentioned to Senator Murphy, we’ll have a hearing next Wednesday on another important part of the Cures Act, which was the first reorganization of our mental health laws in a decade, which Senator Cassidy and Senator Murphy played a major role in. We look forward to that.

Senator Murray and I will each have an opening statement. Then we’ll introduce our panel of witnesses. After our witnesses, each Senator will have 5 minutes of questions. I expect we’ll have a large number of Senators coming and going to this hearing.

In 2007, Doug Oliver, who is in the front row, I believe, a computer programmer, began to have trouble seeing and after a near accident had his driver’s license taken away and was declared legally blind. The culprit was a rare form of Macular Degeneration. Doug moved to Nashville, where his doctor at the Vanderbilt Eye Institute told him that while there were no cures, Doug could search online for a clinical trial.

Doug found a regenerative medicine clinical trial in Florida, where doctors took cells out of the bone marrow in his hip, spun them in a centrifuge, and then injected those into his eye. Three days later, he began to see. His eyesight eventually improved enough to get his driver's license back and enough that he became an effective advocate for more support for regenerative medicine, done the proper way, which we included in the 21st Century Cures Act. Earlier this year, Doug gave me the cane he used while he was blind. He said, "I don't need it anymore." I treasure it, and I keep it in my office, and I thank him for his advocacy, and we hope others have the same advantage.

When Congress passed the 21st Century Cures Act, we hoped to unleash medical innovation and give Americans more access to life-changing treatments and cures so more Americans could experience medical miracles. It is especially appropriate to be having this hearing today because it marks the 1-year anniversary of the Senate passing Cures.

When it became law last December, I said that President Obama had signed a second Christmas miracle. The first one, in 2015, was the Every Student Succeeds Act, the law fixing No Child Left Behind, which came from this Committee. Last year, it was the 21st Century Cures Act, which Majority Leader McConnell called the most important legislation Congress passed last year.

I have often said of the Every Student Succeeds Act that a law is not worth the paper it's printed on if it is not implemented properly. I intend to ensure Cures is also implemented properly. We began our oversight on Cures with a hearing in October on the electronic health records provisions, and, in addition to today's hearing, I mentioned that we will continue our oversight next Wednesday on the mental health provisions.

Today, we are hearing from Dr. Collins and Dr. Gottlieb on the provisions related to biomedical research. We are fortunate to have two such talented leaders who know their agencies, are widely respected in Congress, and capable of getting results. It doesn't always happen. Sometimes you have capable leaders, and they don't have any money, or they don't have new authority. Sometimes you have new authority, new money, and the leaders don't have a clue what they're doing. In this case, we've got new authority, we've got new money, and we've got two of the most capable leaders we could have. So we're delighted with that.

While the legislation included provisions to improve electronic healthcare records, resources to fight the opioid epidemic, and the first update to mental health programs in a decade, the major purpose of the legislation was to provide additional resources and authorities to speed drugs and devices through the research and development process into doctors' offices and patients' medicine cabinets while ensuring the FDA gold standard of safety and efficacy. It is not an overstatement to say that the 21st Century Cures Act has the potential to affect virtually every American family by taking advantage of breathtaking advances in biomedical research.

Dr. Collins, at a Senate Appropriations Subcommittee hearing in 2016, you offered bold predictions—you called them—for future major medical advances if we continue funding the National Insti-

tutes of Health and ensure that the Food and Drug Administration has the tools it needs.

One prediction is that scientists will find ways to identify Alzheimer's before symptoms appear as well as how to slow or even prevent the disease. Alzheimer's causes untold family grief and costs \$259 billion a year. Another prediction of yours was, using a patient's own stem cells, doctors could rebuild his or her heart. This personalized heart would make transplant waiting lists and anti-rejection drugs obsolete and put doctors like former Senator Bill Frist out of business.

[Laughter.]

Dr. Collins, you have made other predictions that—because he was a heart transplant surgeon. Dr. Collins, you made other predictions equally breathtaking: the development of an artificial pancreas for diabetes patients, A Zika vaccine, a universal flu vaccine, an HIV/AIDS vaccine, all available within a decade, and new non-addictive pain medicines to help patients as we continue to battle the opioid crisis that kills 91 Americans every day. You said this week in another hearing that might happen in as soon as 5 years.

The 21st Century Cures Law put in place policies that will fund biomedical research at a time of limitless opportunity to help make Dr. Collins' predictions a reality. Today, we want to find out from Dr. Collins and Dr. Gottlieb, those leading this charge, how implementation of the law is going. For example, Cures included a surge of one-time funding of \$4.8 billion for the NIH, including money for the Precision Medicine Initiative, Cancer Moonshot, and BRAIN Initiative.

I know from talking with Vanderbilt University that the Precision Medicine Initiative—the plan to map the genomes of 1 million volunteers to help researchers develop treatments and cures tailored to a patient's genetics, environment, and lifestyle—has already begun enrolling patients less than 1 year after the program began. In addition to the Precision Medicine Initiative, I am curious about how funding has been spent and when and how you plan to keep Congress informed of your results.

Cures required a process to look at burdensome regulations on researchers. I would like to hear if this is helping researchers spend more of their time and money on research and less on administrative tasks. Cures also put in place policies at the FDA to move safe and effective treatments and cures through the regulatory process more rapidly and at a lower cost.

For example, Senators Burr, Bennet, and Hatch worked on a breakthrough provision for devices modeled after a breakthrough provision for drugs. The first breakthrough approval was just last week for an exciting cancer diagnostic. Senators Isakson and Casey worked on removing red tape from the review of combination products. I worked with Senator Murray to make sure FDA had the authority to hire and pay scientists to keep up with the rapid rate of innovation.

21st Century Cures also added \$30 million to support regenerative medicine and an accelerated pathway for these treatments at FDA so we can hear more stories like Doug Oliver's.

FDA has begun implementing these provisions, and I look forward to hearing how FDA and NIH are working together to make

sure the funding and authorities for regenerative medicine are helping to advance this important work, while ensuring that bad actors do not take advantage of the hope of this exciting field to harm or defraud patients. It is going to be difficult to cover everything today, but I look forward to hearing about the progress being made to unleash medical innovation and bring new drugs and devices to patients.

Senator Murray.

#### OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you so much, Chairman Alexander.

Welcome to our guests today. Thank you for joining us.

Dr. Collins, it's good to have another opportunity this week to talk with you again about the work being done at NIH.

Dr. Gottlieb, welcome to you as well. I'm looking forward to your updates from FDA.

Next week marks 1 year since the signing of the bipartisan 21st Century Cures Act, and as I said at the time of the passage—and I'll repeat it now—as much as this law helped to build on America's tradition of leadership in lifesaving public health initiatives and medical innovation, Cures was really first and foremost about providing hope, hope to the millions of people and families who are impacted by illness and disease; hope for our communities suffering at the hands of the opioid epidemic, for example. Like all of my colleagues, including our guests today, this crisis is something I hear about every day. I have visited with countless communities in my home State of Washington that have been devastated by addiction.

While we know we can and must do more, I'm glad that Cures took an important first step and dedicated over \$1 billion in new funding above and beyond the budget caps to help states and communities fight back against that crisis. We secured important changes to make sure this money went directly to the states that need it the most.

For far too long, our health system has failed patients and families seeking treatment and support. That is why in Cures we prioritized expanding access to quality care for mental illness and substance use disorders, and we strengthened coordination between local agencies engaged in crisis intervention. I'm looking forward to discussing that work further at a hearing we're having next week.

On today's topic, I'm proud of our work on Cures to address head-on some of the hardest to treat diseases by providing nearly \$4.8 billion in funding for the NIH, including support for the Beau Biden Cancer Moonshot and the Precision Medicine and BRAIN Initiatives, all of which I would note are very important to my home state where we are spiriting much of that new research taking place as a result.

Along with these investments, we included provisions in the law to equip NIH with the tools and authorities needed to meet the demands of biomedical research in the 21st Century. We made it a priority to improve the inclusion of women and children and other underrepresented populations in clinical research so that the promise of these initiatives like Precision Medicine are extended to all patients. As part of this work, I championed a provision that creates a task force to better support the evaluation of drugs for preg-



nant and lactating women, and we addressed many of the concerns that have been holding back progress in the research community by supporting young researchers and reducing the red tape.

Cures also made sweeping reforms to FDA, and one of my top priorities was granting the agency greater hiring authority to recruit and retain qualified individuals who understand the latest science and technology, and I'm very interested to get an update from you, Dr. Gottlieb, on how you're filling those positions, especially in light of the hiring freeze that this year was mandated by the President.

We also made sure Cures gave FDA the authority to ensure medical devices, like scopes that caused the outbreak of antibiotic-resistant infections in my home State of Washington, are safe for patients, and we gave more clarity to developers of drug device combination products and codified key provisions in the Prescription Drug User Fee Agreement, including to ensure patients are included in the drug development process.

I'm glad we have the opportunity today to talk about the ongoing implementation of Cures, and I will be very focused on making sure we are committed to strong congressional oversight, rejecting this administration's efforts to roll back and undermine patient protections, and doing more to provide the strong investment needed at NIH and at FDA not just to support cures but also to advance 21st Century science and innovation.

Now, in general, I'm glad that NIH and FDA have been active and timely in implementing the law, including many of the provisions that I just talked about. I'm encouraged by these efforts. I want us to keep moving in the right direction.

Dr. Collins, in light of the extremely concerning direction the Trump administration has taken when it comes to healthcare, especially in regards to women's health, I want to hear more about what NIH is doing to bolster your researchers' work to further science over extreme ideology.

Dr. Gottlieb, during your confirmation hearing, you said that 21st Century Cures is a good roadmap for what you hope to accomplish as Commissioner. I'd like to hear about how you at FDA are pushing back against this administration's deregulatory approach and making sure Cures is being efficiently and faithfully implemented. Specifically, I will be asking more about what FDA is doing to ensure the medical devices patients rely on are safe and effective.

Again, both NIH and FDA have made important steps in implementing and meeting Cures deadlines this year. But we have a lot more deadlines coming up in 2018, and since we know funding remains an issue, I look forward to hearing from each of you on how we can make sure that we're truly putting patients and families first.

Again, welcome to both of you. Thank you for being here.

The CHAIRMAN. Thank you, Senator Murray.

Each witness will have 5 minutes to give his testimony. The first witness we'll hear from is Dr. Francis Collins. He's been Director of the National Institutes of Health, overseeing the work of the largest supporter of biomedical research in the world since 2009. The second witness we'll hear from is Dr. Scott Gottlieb. He's Com-

missioner of Food and Drugs, ensuring our drugs and medical devices are safe and effective. He was formerly Deputy Commissioner of the same agency. He was confirmed on May 9 of this year.

Welcome again to our witnesses. Dr. Collins, let's begin with you.

#### **STATEMENT OF FRANCIS COLLINS**

Dr. COLLINS. Well, good morning, and thank you, Chairman Alexander, Ranking Member Murray, and other distinguished Committee Members. It is an honor to be here today with my colleague, Dr. Scott Gottlieb, the Commissioner of the FDA.

As you well know, the 21st Century Cures Act aimed to catalyze a very important goal shared by all Americans; to speed the pace at which scientific discoveries are translated into lifesaving treatments and cures. We at NIH, actually, greatly appreciate your leadership in passing this bipartisan act by a vote of 95 to 4 in the Senate exactly 1 year ago today, December 7th.

This enhances our authorities and resources in ways that will help us to achieve this goal. Many thoughtful provisions are included in the act, such as reducing administrative burdens so our scientists can devote more of their time to research, expanding our ability to award prizes for exceptionally creative ideas, and strengthening measures to protect patient privacy.

In my written statement, I've submitted a comprehensive report on how NIH has worked quickly to implement the provisions of the act. We are motivated by a sense of urgency to help patients in need of breakthroughs.

In my oral statement, I'd like to focus on the Cures Innovation Fund. Among the vital areas of NIH-supported research being accelerated by this fund are the BRAIN Initiative, the Cancer Moonshot, the Regenerative Medicine Innovation Project, and the Precision Medicine Initiative.

Let's begin with the BRAIN Initiative. This pioneering effort is aimed at revolutionizing our understanding of the most complex structure in the known universe, the human brain. In fiscal year 2017, we leveraged our Cures Innovation Funding with our annual appropriation to launch no less than 110 exciting new brain research projects. Some of these will develop detailed maps of neural circuits. Others will create a census of the cell types in the brain, and still others will create powerful new tools to monitor and modulate brain activity. This will advance efforts to develop new ways of detecting, treating, and even preventing many serious brain disorders, including Alzheimer's Disease, Parkinson's, schizophrenia, autism, drug addiction, epilepsy, traumatic brain injury.

With the help of the Cures Innovation Fund, a second research area, the Cancer Moonshot, is aggressively pursuing a very ambitious goal to accelerate advances in cancer prevention, diagnosis, treatment, and care. To achieve that goal, we must take a variety of innovative steps, and that includes enhancing the research infrastructure by creating a clinical trials network with an unwavering commitment to data sharing and to move cancer treatment programs forward more rapidly.

In another of these innovative moves, NIH recently joined with the FDA and with 12 biopharmaceutical companies to launch the Partnership for Accelerating Cancer Therapies, or PACT. This pub-

lic-private partnership will initially develop biomarkers to speed the development of cancer immunotherapies, an exciting new approach to treatment that enlists the patient's own immune system.

Recently, we have seen some amazing responses to cancer immunotherapy. But we need to bring that kind of success to far more people with more types of cancer and do it quickly. The Cures Innovation Fund, with the support of this Congress, is helping to make that happen.

The Cures Act also provides support for regenerative medicine research. This emerging area of science involves the use of cells and other technologies, such as engineered biomaterials and gene editing, to repair or replace damaged cells, tissues, or organs.

As a result of the Cures Act, NIH has launched the Regenerative Medicine Innovation Project. This project recently made eight clinical research awards covering a broad spectrum of science and technology and going well beyond the funding specifically provided by the Cures Act. Some are focused on common diseases, including diabetes and vision disorders, such as the one that afflicted Doug Oliver that you referred to earlier, while others are aimed at rarer conditions, such as sickle cell disease and idiopathic pulmonary fibrosis.

In partnership with the FDA, we are hosting a major workshop, actually right now, beginning yesterday and going all the way through today, to explore the state of regenerative medicine research involving adult stem cells. Both Scott and I spoke at this workshop at the beginning of it yesterday morning. This conference will inform our future research directions by helping us to identify the areas of greatest scientific and therapeutic promise.

Finally, I want to tell you how thrilled I am that you supported the Precision Medicine Initiative, PMI, by including an authorization and funding in the Cures Act. The centerpiece of PMI is the All of Us Research Program, which will enroll 1 million or more Americans from every walk of life. These volunteers will contribute their health data in many ways over many years to create a research resource that will catalyze a new era of precision medicine.

This is an ambitious goal, and we know that NIH cannot succeed on its own. All across the Nation, NIH is teaming up with the Veterans Administration, health provider organizations, community health centers, a Data Center at Vanderbilt, and other groups to figure out the best ways to recruit participants, especially those that are traditionally underrepresented in biomedical research. NIH has also partnered with five companies to create a Participant Technology Center, and our partners are testing how wearable devices, like the ones I'm wearing today, may provide easy ways for all of us volunteers to contribute data on physical activity, sleep, heart rates, and so on.

Getting all these partners on board would have been nearly impossible had not the Cures Act included Other Transaction Authority, OTA, for PMI, making it possible for NIH to move forward with unprecedented speed and flexibility to carry out beta testing of all the many components, and we are now scheduled to launch fully in the spring of 2018. As someone who grew up in a theater family, I know the value of a dress rehearsal before the curtain goes up.

That's what our beta test is right now. We've enrolled over 10,000 people.

But when the full launch does happen, you and everyone else who supported the 21st Century Cures Act will deserve applause. By the way, if you want to find out more about that, that is the website that will keep you posted. That applause will be not just for all of us, but for each of the many, many ways in which Cures supports the work of the National Institutes of Health, or, as some have called us, the National Institutes of Hope, as Senator Murray recently referred to.

Speaking of hope, let me then just conclude with a favorite exhortation from the British poet, Peter Levi: Hope in every sphere of life is a privilege that attaches to action. No action, no hope.

Thank you for your action in enacting the Cures Act. I'll be happy to take your questions.

[The prepared statement of Dr. Collins follows:]

PREPARED STATEMENT OF DR. FRANCIS S. COLLINS

Chairman Alexander, Ranking Member Murray, and Distinguished Members of this Committee, thank you for hosting this important hearing.

More so, thank you for creating the need for this hearing—for the 21st Century Cures Act (Cures Act) which was enacted 1 year ago. The Cures Act touches on so many important issues. From providing support for four cutting edge research priorities, to enhancing privacy protections to inclusion of various communities in research trials, to reducing administrative burden to expanded prize authority, we at NIH appreciate your leadership and dedication in enacting new authorities to speed the pace of research and improve how science is conducted to transform the way we translate discovery into therapies.

In my testimony, I will highlight how NIH is implementing some of the key provisions of the Cures Act and how it is benefiting the biomedical research community and, most importantly, patients.

**Big Data: The Promise of Data Sharing Balanced With the Need for Privacy**

As in most fields, computing power is changing the way research is done. The promise of big data cannot be overstated for finding patterns of disease and health and targeting therapeutics to sub-populations. The Congress, in the Cures Act, wisely recognized both the potential and the risks inherent in sharing data sets and NIH has moved quickly to get the appropriate protections in place.

First, on September 7th, NIH issued a Guide Notice to our research community implementing the significant enhancements this Committee made to the Certificates of Confidentiality, making them both automatic and compulsory. To implement this change while minimizing the burden to our researchers, we streamlined the issuance of Certificates into the terms and conditions of every research award we make involving human subjects.<sup>1</sup> Since October 1st, every NIH award has this added layer of protection for research participants.

Second, on September 17th, guidance on the FOIA exemption for genomic information was disseminated to all NIH FOIA officers.

Only now that the new Cures Act privacy protections are in place, are we moving forward on the exciting new authority to require data sharing. This will be a sea change in biomedical research so we must be deliberate about how to measure the usefulness of data sets, where shared data should be stored, how patient protections are insured, how interoperability is achieved, and what tools researchers most need in the shared environment. On November 6th, NIH made 12 awards in a Data Commons Pilot to answer just these kind of questions. We selected three prominent NIH datasets researchers can use to test their processes. The biomedical research community will be watching this pilot program very closely.

<sup>1</sup> <https://humansubjects.nih.gov/coc/index>.

### Inclusion

We've made tremendous progress in managing diseases through the development of new drugs and devices over the years that were tested in clinical trials. But trials haven't always included the full spectrum of humanity, and this limits the applicability of study results. It also limits our ability to target therapies and address disparities. Congress helped NIH address this issue through the Cures Act in three focus areas: inclusion of children and seniors; inclusion of pregnant and lactating women; and continuing our focus on women, and racial and ethnic minorities.

On June 1-2, 2017, as required by the Cures Act, NIH held a workshop on inclusion across the lifespan. It might seem easy to include all age ranges but both children and older adults require special considerations. At the workshop, investigators with expertise in conducting clinical studies with pediatric and older populations, ethics experts, and other stakeholders had a robust discussion about barriers and facilitators to the inclusion of volunteers of all ages in research. The findings and recommendations will be presented at my Advisory Committee meeting on December 14-15, 2017, and we will determine what policy changes are needed to ensure individuals across the lifespan are appropriately included in clinical research.

The Cures Act also asks NIH to continue making progress on the inclusion of women and ethnic and racial minority populations in research. This has been a partnership of the Congress and NIH for many years—the Congress authorized both the NIH Office of Research on Women's Health and what is now the National Institute on Minority Health and Health Disparities in 1993. With the help of the Congress and the Cures Act, we continue to improve. We are now collecting inclusion data on a study-by-study basis and in the coming year NIH will report, for the first time, inclusion data from studies on a disease and condition basis. At the December meeting, the expert Advisory Committee will have a public discussion of recommendations for further advancing the field and updating our inclusion guidelines. I look forward to the conversation and I will be happy to update you as decisions are made.

Finally, the Cures Act created a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women.<sup>2</sup> This area of research is vital, but it is absolutely critical that we carefully consider intentional exposures in this potentially vulnerable time of life. NIH established PRGLAC on March 13, 2017, bringing together Federal and non-Federal experts, including the Food and Drug Administration, representatives from relevant medical societies, non-profit organizations, and industry, to discuss these important issues.

PRGLAC has already held two meetings—the first on August 21-22, 2017, to determine the scope of current Federal activities on safe and effective therapies for pregnant and lactating women, and the second on November 6-7, 2017, to understand the ethical issues surrounding research to develop therapies for pregnant and lactating women. The third meeting on February 26-27, 2018, will be on communication strategies for health care providers and the public about the use of therapies for pregnant and lactating women, and the fourth meeting on May 14-15, 2018, will be on recommendations to address the gaps in knowledge, ethical issues, and communication strategies for therapies used by pregnant and lactating women.

Based on the outcome of the Task Force meetings, a report with recommendations will be developed for the HHS Secretary. NIH is grateful to the Congress for recognizing the need for careful consideration in this area of research and looks forward to addressing any recommendations made by the Task Force.

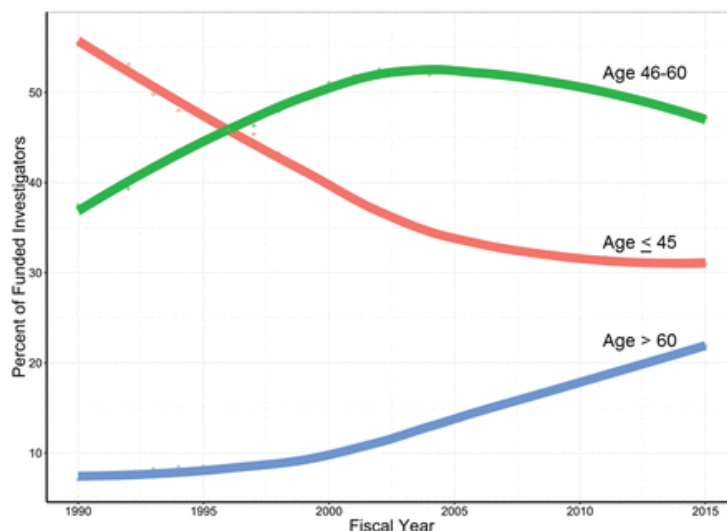
### Strengthening Biomedical Workforce

NIH and its stakeholder community have for many years been concerned about the long-term stability of the biomedical research enterprise. As a consequence of NIH's loss of more than 20 percent of its purchasing power from 2003 to 2015, researchers were forced to vie for limited resources, leading to a hypercompetitive environment. With success rates below 20 percent, many highly meritorious applications continue to go unfunded. This has too often resulted in misaligned incentives and unintended consequences for talented researchers at all career stages who are trying to succeed and stay in science. The current environment is particularly challenging for many new-and mid-career investigators.

Over the last several years, NIH has taken numerous steps to balance, strengthen, and stabilize the biomedical research workforce, but these measures have only

<sup>2</sup> <https://www.nichd.nih.gov/about/advisory/PRGLAC/Pages/index.aspx>.

taken us so far. While the percentage of NIH awards that support early career investigators has gone from declining to flat, these gains have been offset by a decline in the percentage of NIH awards that support mid-career investigators.



As a direct result of the Cures Act, in June 2017, NIH launched the Next Generation Researchers Initiative<sup>3</sup> aimed at strengthening the biomedical workforce with a focus on early career investigators or investigators who are at an early stage in their career. NIH intends to take a multi-pronged approach, which we outlined in an article published on November 7, 2017,<sup>4</sup> to increase the number of NIH-funded early stage and mid-career investigators and to stabilize the career trajectory of scientists.

NIH will develop evidence-based, data-driven strategies to assure that NIH investments are directed in ways that maximize scientific output. Institutes and Centers will also place greater emphasis on current NIH funding programs to identify, grow, and retain new-and mid-career investigators across these critical career stages. The NIH Office of the Director will track progress across ICs and assess if these strategies are working. I am personally committed to this issue and thank the Committee for their support of early and mid-career investigators.

#### **System Innovation: Reducing Administrative Burden and Increasing Efficiency**

Policies generated with the best intentions sometimes have serious adverse consequences for research. The Cures Act included numerous provisions that cut the bureaucratic red tape that slows the progress of science. It also provided NIH with new authorities to improve efficiencies and speed up the discovery process.

The Cures Act included provisions to improve ClinicalTrials.gov. ClinicalTrials.gov is a data base of privately and publicly funded clinical studies conducted around the world that plays a crucial role in ensuring the transparency and accountability to the public of researchers and their sponsors. In addition, this resource is used by researchers to stay up-to-date on developments in their field, find collaborators, and identify unmet needs, and it is also used by patients and families to search for potential studies to enroll in or learn about new treatments that are being tested. NIH strives to make this resource as user friendly as possible so it can benefit researchers, patients, and their families, and the Cures Act is helping in several ways.

First, the Cures Act made technical fixes to the legislation establishing ClinicalTrials.gov that ensure NIH is able to capture more clinical trials in the system and improve our oversight and transparency. Second, it required NIH to consult

<sup>3</sup> <https://grants.nih.gov/ngri.htm>.

<sup>4</sup> Michael Lauer, Lawrence Tabak, and Francis Collins, "Opinion: The Next Generation Researchers Initiative at NIH," *PNAS*, 114 (2017): 11801–11803.

with relevant Federal agencies and other stakeholders to receive recommendations to enhance ClinicalTrials.gov's usability, functionality, and search capability. In February 2017, the National Library of Medicine (NLM), along with 18F, a digital services consultancy within the General Services Administration, began conducting user research on ClinicalTrials.gov with a range of stakeholders. As a result of this work, NIH rolled out a first in a series of changes to ClinicalTrials.gov on June 19, 2017. On September 25, 2017, NLM released more updates as the next phase in its ongoing effort to enhance the functionality of the data base. In response to the Cures Act, NLM will work continuously to make it easier for users to find and participate in clinical trials.

In an effort to improve efficiency, the Cures Act provided a new EUREKA prize authority and allowed NIH to use Other Transactions Authority (OTA) in two areas that need extra flexibility and collaboration: the Common Fund and the All of Us Research program, part of the NIH Precision Medicine Initiative.

The EUREKA prize authority is being implemented in three ways:

- On November 2d, the National Institute on Aging issued a request<sup>5</sup> for public input on (1) the feasibility of three potential prize competitions focused on Alzheimer's disease (AD) and related dementias (ADRD): Validating predictors of AD progression; PET radiotracer to measure in vivo synaptic integrity; and low cost innovation of improving systems of care for AD/ADRD patients and caregivers; and (2) any other suggestions on AD/ADRD research goals to connect to a prize. Comments are due on December 31, 2017.
- NIH formed the EUREKA Prize Coordination Committee to review future proposals for future EUREKA prize competitions.
- NIH funded the National Academy of Sciences (NAS) to study Innovation Prizes and Federal R&D with specific emphasis on strategies to determine which "EUREKA" prize topics are consistent with congressional intent. The NAS study will also consider the strengths and weaknesses of various measures of health outcomes and effects on government expenditures. The NAS intends to hold a workshop in 2018.

OTA is integral to our exploration of how best to structure data sharing, known as the Data Commons Pilot Phase,<sup>6</sup> which was announced on November 6th. The goal of the NIH Data Commons is to accelerate new biomedical discoveries by providing a cloud-based platform where investigators can store, share, access, and compute on digital objects (data, software, etc.) generated from biomedical research and perform novel scientific research including hypothesis generation, discovery, and validation. The use of OTA awards allows flexibility for the awardees to work together to design innovation solutions that meet the computational and scientific needs of the Pilot.

The *All of Us* Research Program aims to enroll one million individuals in a decades-long research project. That ambitious goal requires flexibility, complex and dynamic interactions, and ways to engage non-traditional NIH awardees to advance the mission. For example, All of Us has used OTA to make awards to the Healthcare Provider Organizations to help build the research protocols, test enrollment procedures, and collect essential health data and biological specimens.

The Cures Act also recognizes that two of the cornerstones of scientific advancement are rigor in designing and performing scientific research and the ability to reproduce biomedical research findings. In recent years, the scientific community has become aware of the need to improve rigor and reproducibility. In 2014, NIH worked with scientific publishers to develop a set of principles and goals that 79 publishers have now endorsed. As the Cures Act requires, my Advisory Committee has convened a Working Group on Rigor and Reproducibility and they are reviewing the experience of the last few years, leading to the development of recommendations for a formal policy. I look forward to updating you as this effort takes shape.

### NIH Innovation Fund

Last, but certainly not least, the Cures Act provided multi-year funding through the NIH Innovation Fund for four highly innovative scientific research initiatives: the Precision Medicine Initiative (PMI), the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the Cancer Moonshot, and the Regenerative Medicine Innovation Project. As required by the Cures Act, on March 28th, I solicited recommendations from my Advisory Committee on how to allocate

<sup>5</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-AG-17-018.html>.

<sup>6</sup> <https://commonfund.nih.gov/bd2k/commons/awardees>

the funds. We had a robust conversation about each of the initiatives and the Advisory Committee members provided critical advice on how to move forward. As a result of that discussion, and conversations with my NIH colleagues, we drafted the NIH Innovation Fund Work Plan,<sup>7</sup> which was submitted to Congress in September 2017, outlining how the agency will use the NIH Innovations Funds for each of these four initiatives. I would like to tell you a bit about each of these initiatives and how the NIH Innovation Funds are helping to move each initiative forward.

### **The Precision Medicine Initiative**

Precision medicine is a revolutionary approach for disease prevention and treatment that takes into account individual differences in lifestyle, environment, and biology. While some advances in precision medicine have been made, the practice is not in use for most diseases. The All of Us Research Program, a key element of PMI, is building a national resource—one of the world’s largest, most diverse biomedical data sets in history—to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care. All of Us will engage one million or more U.S. volunteers from all life stages, health statuses, races/ethnicities, and geographic regions to reflect the country’s diverse places and people to contribute their health data over many years to improve health outcomes, fuel the development of new treatments for disease, and catalyze a new era of evidence-based and more precise preventive care and medical treatment.

Across the Nation, NIH has engaged 10 large health provider organizations, six community health centers, and the Veterans Administration to be our partners in this ambitious study. The program is launching in stages. The beta phase began in May 2017 during which each of our partners are testing their systems and processes to ensure a good experience for participants.

In July 2017, the program made its first four community partner awards to motivate diverse communities to join and remain in the program, with a focus on those traditionally underrepresented in biomedical research. Each of these organizations has deep, trusted relationships within and ties to their communities, and we are so very pleased to have the opportunity to partner with them to enhance our outreach into communities that have traditionally been underrepresented in biomedical research. NIH has also engaged with organizations to create mobile apps to enroll, obtain consent from, collect data from, and communicate with All of Us participants. One of our partners is working with FitBit on a pilot that will start in mid-2018 to test out ways for participants to easily and efficiently contribute data on physical activity, sleep, heart rates, and other behavioral health information.

We anticipate to roll out nationally in spring 2018. Following the national launch, we will make continuous improvements and updates to the program based on participant feedback and emerging scientific opportunities and technological advances. The Cures Act Innovation Funds will be critical to ensuring the success of All of Us and the promise of personalized medicine.

### **The BRAIN Initiative**

The BRAIN Initiative is aimed at revolutionizing our understanding of the human brain, the most complex structure in the known universe. Launched in 2013, this large-scale effort will push the boundaries of neuroscience research and equip scientists with insights necessary for treating a wide variety of brain disorders. By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. Long desired by researchers seeking new ways to treat, cure, and even prevent brain disorders, this picture will fill major gaps in our current knowledge and provide unprecedented opportunities for exploring exactly how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought.

NIH leveraged the Cures Act’s fiscal year 2017 Innovation Funds, in addition to our annual appropriation, to launch 110 exciting new research projects.<sup>8</sup> These projects are focused on developing detailed brain circuit maps and powerful new tools to monitor and modulate brain activity in animal models to benefit patients with neurological and psychiatric disorders. Understanding the way the brain proc-

<sup>7</sup> <https://www.nih.gov/sites/default/files/research-training/initiatives/nih-cures-innovation-plan.pdf>.

<sup>8</sup> <https://www.braininitiative.nih.gov/funding/fundedAwards.htm>.



esses information and how it lays down memories and retrieves them will be instrumental for understanding brain health, and ultimately, preventing brain disorders such as Alzheimer’s disease, Parkinson’s, schizophrenia, autism, drug addiction, and traumatic brain injury. These awards add to work already underway to give us a high-resolution picture of the circuits and networks in the brain, how they work, and where they can go wrong.

### **The Cancer Moonshot**

The Cancer Moonshot,<sup>9</sup> funded in the Cures Act, has an ambitious goal: to dramatically speed advances in cancer prevention, diagnosis, treatment, and care. The National Cancer Institute (NCI) solicited direct input from the public and convened a Blue Ribbon Panel (BRP) of the Nation’s top cancer researchers, oncologists, patient advocates, and private-sector leaders. In September 2016, the BRP presented its report outlining ten ambitious and achievable recommendations to the NCI’s National Cancer Advisory Board. These recommendations shape the scientific blueprint of the Cancer Moonshot representing areas of research that are poised to accelerate our understanding of cancer and bring benefit to patients. Overall, the recommendations create a vision for future cancer research and treatment in which:

- Researchers can identify possible targets for the development of new cancer treatments and preventive interventions, including immunotherapy and immunoprevention, and learn more about how to avoid or overcome cancer drug resistance in patients;
- Diverse groups of patients contribute information about their cancer, obtain a genomic profile, learn what treatments might work best given their profile, and identify clinical trials that may be appropriate for them;
- Infrastructures are established so that health care providers and researchers can share, access, and analyze information that improves the understanding of how tumors evolve, better predicts treatment outcomes, and helps control patient symptoms and side effects.

Some of these goals are scientific in nature, and some are systemic. If we are to speed advances, we cannot simply do more of the same. We must transform the way we conduct research, the way we share results, and the way we get discoveries into patient care. In fiscal year 2017, NIH made 142 Cancer Moonshot awards, including efforts to leverage advances in immunotherapy, understand drug resistance, and develop of new technologies to characterize tumors and test therapies. These national and international collaborations will drive discovery for cancer patients and their families. I would like to highlight one of those collaborations for you today.

On October 12, 2017, NIH and 11 leading biopharmaceutical companies launched the Partnership for Accelerating Cancer Therapies (PACT), a 5-year public-private research collaboration totaling \$215 million as part of the Cancer Moonshot.<sup>10</sup> PACT will initially focus on efforts to identify, develop, and validate robust biomarkers—standardized biological markers of disease and treatment response—to advance new immunotherapy treatments that harness the immune system to attack cancer. We have seen dramatic responses from immunotherapy, often eradicating cancer completely for some cancer patients. We need to bring that kind of success—and hope—to more people with more types of cancers, and we need to do it quickly. A systematic approach like PACT will help us to achieve success faster.

With the support of the Congress, the Cancer Moonshot will transform the way cancer research is conducted and ensure that substantial progress is made for patients and their families.

### **The Regenerative Medicine Innovation Project**

Regenerative medicine is an emerging area of science that holds great promise for treating and possibly even curing a variety of injuries and diseases. Regenerative medicine includes using stem cells and other technologies, such as engineered biomaterials and gene editing—to repair or replace damaged cells, tissues, or organs. Stem cell-based approaches are under development in labs around the world, and some have already moved into clinical trials. Such progress notwithstanding, much work remains to be done toward the development of safe and effective regenerative medicine interventions to realize the full potential of this field.

<sup>9</sup> <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative>.

<sup>10</sup> <https://www.nih.gov/news-events/news-releases/nih-partners/leading-biopharmaceutical-companies-accelerate-development-new-cancer-immunotherapy-strategies-more-patients>.

As a result of the Cures Act, NIH launched the Regenerative Medicine Innovation Project to support clinical research on adult stem cells while promoting the highest standards for carrying out scientific research and protecting patient safety. The \$2 million Cures provided for this initiative in fiscal year 2017 were amplified through matching funds and NIH Institute contributions to reach a total of just under \$5 million. In September, NIH made eight clinical research awards<sup>11</sup> that cover a broad spectrum of science and new technologies, and have the potential to advance understanding and treatment of common diseases—including diabetes, anemia, corneal and other eye diseases, and chronic skin ulcers—as well as rare diseases, including idiopathic pulmonary fibrosis, inherited skin diseases, and sickle cell disease.

Several awards will explore the use of adult stem cells to make specialized cells and tissues that could help reduce the need for whole organ transplants or otherwise restore normal function. Others aim to develop reliable methods of generating red blood cells and platelets in the lab to improve the safety and supply of blood available for transfusion.

NIH looks forward to the opportunity the Cures Act provides to advance this field of science and is hosting a workshop on December 6–7, 2017,<sup>12</sup> to explore the state of regenerative medicine science involving adult stem cells, with a focus on approaches for the development of safe and effective products. This will help inform our funding decisions in future fiscal years.

### Conclusion

Thank you for your leadership and dedication that resulted in enacting the Cures Act 1 year ago. Over the past year, the Cures Act has provided NIH with critical resources and tools to advance our mission—to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. We appreciate Congress’s support for NIH through the Cures Act and will continue to implement the law to accelerate scientific discoveries and benefit patients.

The CHAIRMAN. Thank you, Dr. Collins. I hope sometime during the Q and A, you’ll have a chance to comment on your belief that the Other Transactions Authority, which you already have, would be helpful in other areas to help us get where we all want to go.  
Dr. Gottlieb.

### STATEMENT OF SCOTT GOTTLIEB

Dr. GOTTLIEB. Thanks a lot, Chairman Alexander, Ranking Member Murray, and Members of the Committee. Thank you for the invitation to testify at this hearing to discuss the implementation of the 21st Century Cures Act.

Cures set FDA on a transformative path. It set out to optimize our investments in science by modernizing how FDA oversees breakthrough technologies. You asked us to advance innovations more efficiently while maintaining our gold standard for protecting patients. This focus on innovation couldn’t come at a better time. Across multiple fields of science, we stand at an inflection point in medicine where new technology is creating foundational opportunities to treat and cure disease in ways that weren’t possible just a short time ago.

Take, for example, our recent experience with gene therapy. We have seen two recent approvals of CAR-T therapies for cancer where a patient’s own immune cells are reengineered using the tools of gene therapy to target a patient’s individual cancer. This form of gene therapy represents a whole new paradigm in treating

<sup>11</sup> <https://www.nih.gov/rmi/fy-2017-funded-awards>.

<sup>12</sup> <https://www.nih.gov/research-training/medical-research-initiatives/cures>.

cancer, and the early results are changing the way we treat serious tumors.

This experience shows how a single fundamental breakthrough in science can open up a whole new way of combating disease. In gene therapy, that breakthrough has been the development of vehicles that can deliver genes more efficiently to their target inside the body. These are often referred to as vectors, and they've taken the form of viruses that are specifically engineered for this purpose.

In particular, the advent of a specific kind of largely inert adeno-associated virus, or AAV vector, was an inflection point in this field. I liken the advent of the AAV vectors to the development of processes for making antibody drugs and making these medicines nearly identical to fully human cells that they were mimicking.

Monoclonal antibodies represented a promising field of potentially breakthrough medicines in the 1990's, but for a long time, these therapeutic drugs fell short of their promise. That was because these drugs were made with antibodies from mice, and the antibody drugs themselves were soon rejected by patients' immune systems. Then came the science for humanizing these antibodies so they would more fully mimic the normal human counterparts, and pretty soon, we saw many breakthrough drugs as a result. A whole new field of medicine grew up very fast.

I believe we're at a similar turning point when it comes to gene therapy. Over the next several years, we'll see this approach become a mainstay of treating and probably curing a lot of our most devastating and intractable illnesses. At FDA, we're focused right now on establishing the right policy framework to capitalize on this scientific opening.

Researchers at MIT recently estimated that about 40 gene therapies might win FDA approval by the end of 2022 from a current pipeline of 932 development candidates. They estimate that 45 percent of total gene therapy drugs are expected to target cancer. I can't affirm their estimate, but I can confirm that we're at the early stages of a transformation in medical treatment as a consequence of this new technology, and the benefits are likely to accelerate quickly.

The advance of this field is not risk free. Yet there are good examples of how FDA's embrace of the Cures Act and our effort to build on what Congress set out to do in balancing safety with scientific promise is expanding our ability to capitalize on this breakthrough innovation. In this case, Cures provided a pathway for certain regenerative medicine products to receive expedited review by FDA through the RMAT designation. We extended that opportunity.

FDA has considered CAR-T products to be a form of gene therapy since the key therapeutic manipulation that's made to the cells is through a gene product delivered by a vector. In FDA's new draft guidance on expedited programs for regenerative medicine therapies for serious conditions, FDA clarified that regenerative medicine therapies would include gene therapies that lead to durable modifications of cells and tissues, including genetically modified cells. This would include CAR-T products when these gene therapy products lead to a durable modification of cells and tissues and, therefore, deliver a sustainable effect in the body.

For example, if a gene therapy alters tissue to allow the body to express certain therapeutic proteins, or if a CAR-T cell has resiliency and maintains its presence and delivers a sustainable therapeutic effect, we would consider them to be regenerative medicine therapies. By FDA taking these science-based decisions, it means that gene therapies, including CAR-T, may be eligible for the RMAT designation.

Next year, we'll be building on these opportunities. We'll begin issuing a suite of disease specific guidance documents on the development of specific gene therapy products. We intend to lay out modern and more efficient parameters, including new clinical measures for the evaluation and approval and review of gene therapy for different high-priority diseases where the platform is being targeted. We plan to focus the first guidance document on the use of gene therapy in hemophilia.

Other documents will address clinical areas where there's a lot of interest in using these techniques, such as certain more common single gene disorders. We'll provide innovators with advice and development pathways, including potential accelerated approval endpoints.

Gene therapy is just one opportunity in transforming medicine. This year, FDA may be on track to approve the highest or second highest number of novel medicines across our combined biologics and drug centers in FDA's entire history. We'll also approve the highest number of generic medicines ever, and we're on pace to approve the highest number of novel medical devices in our modern history, all this year, all at one time.

The result of these benefits is measured in product approvals and in some important and some highly novel medicines like the gene therapies. But, ultimately, it's measured in its human impact.

I look forward to answering your questions, and on behalf of my colleagues at FDA, I want to thank you for your support of our mission.

[The prepared statement of Dr. Gottlieb follows:]

PREPARED STATEMENT OF DR. SCOTT GOTTLIEB

Chairman Alexander, Ranking Member Murray, and Members of the Committee: Thank you for the opportunity to testify today on FDA's implementation of the 21st Century Cures Act (Cures Act), almost 1 year after the law's enactment.

The Cures Act was a significant legislative achievement that coincided with a distinctive moment in medicine and technology. This legislation grew out of a bipartisan, bicameral recognition that we are at a moment in science when we have more opportunity to fundamentally alter the course of many human ailments and even cure diseases or reverse the effects of injury and illness.

The Cures Act includes provisions that have the potential to impart far-reaching effects on scientific advancements in medical product development. The new law complements many efforts underway at FDA, all aimed at transforming the way we support product development and marketing authorization and solidifying FDA's gold standard for safety and effectiveness.

**Implementation Overview**

The Cures Act provides the Agency with important tools that help us continue to meet our mission to protect and promote the public health. As such, it has been a top priority of mine to ensure timely implementation so patients can realize the benefits of this new law. By providing product developers a clear and predictable path for new advances, patients and consumers can realize the benefits of innovations while maintaining confidence that the resulting medical products are safe and effective.

The aim of these policies is to improve patient access to innovative medical products while continuing to protect those who rely on these products. The provisions help FDA in its commitment to continue taking a fresh look at how we regulate products developed through truly novel medical advances to ensure that FDA is encouraging their development and creating efficient, risk-based pathways.

Our implementation of the Cures Act has been integrated into our broader agency efforts. From day one, FDA has worked across medical product centers and offices to fully implement the law and build on its provisions. FDA's headway in pursuing the opportunities enabled by the Cures Act illustrates the Agency's enthusiasm and commitment to the spirit and letter of the law's provisions.

Practically, we have facilitated this through the creation of an intra-agency steering committee to ensure a coordinated approach to implementation. This steering committee, working with subject matter experts in the relevant Centers and offices, helps guide the Agency's timely implementation of the Cures Act provisions. It is led by FDA Office of Commissioner staff ensuring a high-level focus on the implementation of the Cures Act.

The steering committee's first task was to develop the Agency's required work plan to explain the approach we intended to take to implement certain provisions of the Cures Act, both now and in future years. The resulting work plan lays out our vision for the \$500 million in authorized new funds over 9 years, if appropriated, that is included in the law.<sup>1</sup> The steering committee also conducted an analysis of the law's provisions and compiled a list of all FDA-related requirements. The steering committee uses these documents to ensure transparency with the public on our progress by maintaining a website on the Cures Act, as well as a public tracker of deliverables required by the Cures Act. The current tracker lists our commitments and progress toward fulfilling them.<sup>2</sup> This public information allows a wide range of stakeholders to keep up with our implementation efforts.

We also have worked with our colleagues at the Department and other Health and Human Services (HHS) agencies, such as the National Institutes of Health (NIH), to implement crosscutting provisions. For example, FDA's Office of Women's Health has collaborated with NIH and others on the Task Force on Research Specific to Pregnant Women and Lactating Women to help improve the availability of information available to providers and patients for making evidence-based treatment decisions.

Throughout the implementation process, FDA has utilized our new authorities in the Cures Act to pursue new ways to improve the climate for innovation and advance products to those who need them. In doing so, we have challenged ourselves to look at how we can make the development process more efficient by modernizing our processes and removing obstacles that add to time and cost without meaningfully improving our knowledge about safety and effectiveness.

### Implementation Updates

#### ONCOLOGY CENTER FOR EXCELLENCE

One of our first achievements under the Cures Act was to stand up FDA's new Oncology Center for Excellence (OCE). The OCE marks a shift in FDA's traditional operating structure. It creates cross-center teams to work together to examine products to treat cancer. Rather than focusing on the primary mechanism of action, or on the kind of product platform being used, teams are grouped based on their deep understanding of the disease.

This approach to product review already has had an impact in the setting of oncology—in August, FDA approved the first cell-based gene therapy ever in the U.S. to treat certain children and young adults with B-cell acute lymphoblastic leukemia. A second product to treat adult patients with certain types of large B-cell lymphoma was approved in October. Both products had clinical reviews conducted by the OCE, while our Center for Biologics Evaluation and Research (CBER) conducted all other aspects of review and made the final product approval determinations.

This is an organizational model that we seek to adopt in other settings. We are evaluating the creation of additional disease-specific offices as part of a more modern approach to the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER). Some of the areas under consideration are immunology and

<sup>1</sup> The Cures Act Work Plan can be accessed here: <https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/UCM562852.pdf>.

<sup>2</sup> The Cures Act Deliverables Tracker can be found on our Cures Act webpage and accessed here: <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/ucm562475.htm21>.

neuroscience. The goals are to provide stakeholders with a single point of contact and to foster synergies and surge capacity across different offices.

### **Minimal Risk Clinical Investigations**

Another cross-cutting initiative has been to produce guidance related to section 3024 of the Cures Act. This section provides FDA with the authority to permit an exception from informed consent for minimal risk clinical investigations when specific criteria are met. Our medical product centers for biologics, drugs, and devices partnered with our Office of Good Clinical Practice and Office of Counterterrorism and Emerging Threats to issue a final guidance related to this provision in July. The guidance will facilitate the conduct of certain minimal risk clinical investigations that are important to address significant public health needs without compromising the rights, safety, or welfare of human subjects.

### **Regenerative Medicine**

One of the most promising new fields of science and medicine is the area of cell therapies and their use in regenerative medicine. These new technologies, most of which are in early stages of development, hold significant promise for transformative and potentially curative treatments for some of humanity's most troubling and intractable maladies.

The Cures Act recognized these opportunities and highlighted the need to establish enhanced pathways for these promising therapies. Immediately after the law passed, CBER moved quickly to establish the Regenerative Medicine Advanced Therapy (RMAT) designation program, as authorized in section 3033. This program aims to facilitate an efficient development program, expedited review of innovative regenerative medicine therapies, and provide more timely access to potentially life-saving products. Products granted designation are eligible for increased early interactions with FDA, including all the benefits available to breakthrough therapies. As of October 31, FDA had granted 11 RMAT designations.

Building on these activities, a few weeks ago, FDA announced the Agency's Comprehensive Policy Framework for Regenerative Medicine. The framework clarifies the Agency's current risk-based, flexible regulatory approach and implements provisions of the Cures Act related to regenerative medicine through a series of two final and two draft guidance documents. When finalized, the draft guidances will further assist in the development of innovative regenerative medicine therapies. The first draft guidance document addresses expedited programs for regenerative medicine therapies products, including the new RMAT designation program, while the other addresses devices used in recovery, isolation, or delivery of RMAT products.

In particular, the draft guidance on expedited programs describes regenerative medicine therapies eligible for RMAT designation as including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using certain such therapies or products, as well as gene therapies that lead to a durable modification of cells or tissues (including genetically modified cells). For example, CAR-T products, which represent a durable modification to certain T-cells of their recipients, have been considered by FDA to be a form of gene therapy. Therefore, RMAT designation is available to CAR-T products that meet the other criteria for designation.

CBER is also working to facilitate an effort to coordinate and prioritize the development of standards and consensus definitions of terms to support the development, evaluation, and review of regenerative medicine therapies and regenerative advanced therapies, including with respect to the manufacturing processes and controls of such products. In September 2017, FDA awarded a contract to support the coordination and development of these standards and consensus definitions through a public process, in consultation with the National Institute of Standards and Technology and other stakeholders.

### **Digital Health**

FDA also is working to implement the digital health provisions of the Cures Act. Earlier this summer, FDA released an action plan that included the Agency's precertification pilot program, which explores how to apply a tailored, risk based approach toward digital health technology by looking at the software developer or digital health technology developer rather than primarily at the product. The Cures Act expands on policies advanced by FDA's Center for Devices and Radiological Health (CDRH) and makes clear that certain digital health technologies—such as clinical administrative support software and mobile apps that are intended only for maintaining or encouraging a healthy lifestyle—generally fall outside the scope of FDA

regulation. Such technologies tend to be low risk but can provide great benefits to patients and to the health care system by helping keep patients and consumers more informed and engaged in their health. In the coming months, FDA will publish guidance to further clarify what falls outside the scope of FDA regulation and to explain how the new provisions affect pre-existing FDA policies.

In late October, the Agency issued the “510(k) Software Modifications” guidance—the first of several guidance documents clarifying our policy in this space. FDA will also provide guidance to clarify the Agency’s proposed position on products that contain multiple software functions, where some functionalities fall outside the scope of FDA regulation, but others do not. In addition, FDA will provide new guidance on other technologies that, although not addressed in the Cures Act, present low enough risks that FDA does not intend to enforce certain pre-market regulatory requirements. Greater certainty regarding the types of digital health technology that are subject to regulation and more clarity on FDA’s compliance policies will not only help foster innovation, but also will help the Agency to devote its resources to higher-risk priorities.

### **Breakthrough Devices Program**

While FDA is taking steps to improve efficiency in all our review programs, the Agency is especially committed to helping devices that fill an unmet need move through the process as efficiently as possible. The Cures Act gave FDA new authorities to help achieve this goal. The Agency has issued a draft guidance regarding a new Breakthrough Devices Program, which was created by the Cures Act. Building on our Expedited Access Pathway program, which had been in place since 2015, the Breakthrough Devices Program is intended to help patients have more timely access to certain devices that more effectively diagnose or treat life-threatening or irreversibly debilitating diseases or conditions, such as technologies with no alternative or that offer a significant advantage over existing FDA-cleared or approved alternatives.

As described in the draft guidance, the program would enable a more agile pre-submission process for breakthrough devices. Breakthrough device innovations that are highly novel can also be more complex to assess. Thus, earlier and more frequent interaction between FDA and manufacturers should allow manufacturers and the Agency to make the best use of resources to bring novel medical technologies to the market more quickly.

### **510(k) Modifications**

Many devices undergo modifications based upon feedback from medical professionals, patients, and other users who help innovators make adaptations to improve a device’s performance. A regulatory framework that responds quickly to iteration is key to improving device safety and performance.

FDA finalized two guidance documents on device modifications in October. They are designed to help innovators determine when they need to submit a new pre-market notification (510(k)) prior to making a change to a legally marketed device subject to 510(k) requirements. The final guidance documents will help innovators introduce iterative improvements that can improve a product’s safety and performance by establishing more predictable, consistent, and transparent criteria regarding when FDA needs to review and clear changes.

These new guidance documents do not change FDA’s review standard. Instead, the new guidances enhance predictability and consistency for innovators deciding when to submit new 510(k)’s by better describing the regulatory framework, policies, and practices underlying such a decision.

This improved clarity will help reduce the barriers to beneficial innovation and improve patient care by reducing unnecessary submissions to FDA for changes that could not significantly affect device safety or effectiveness, so patients can benefit from enhancements more quickly.

### **510(k) Exemptions**

Under provisions of the Cures Act, FDA exempted more than 70 Class I device types and more than 1,000 Class II device types from the requirement to submit to FDA a 510(k) submission. This Cures directive is part of our ongoing strategy to decrease regulatory burdens on the development of beneficial technologies and reduce the costs of innovation. Device types that are exempt from 510(k) are not generally exempt from other regulatory controls (such as current good manufacturing practice requirements, adequate and proper packaging and labeling, and registration and listing), which ensures consumers can continue to rely on the Agency’s

oversight of these products while giving FDA more capacity to focus its oversight on higher risk products.

### **Modernizing Review of Reusable Devices**

The Cures Act also provided FDA an important authority to require instructions for use and validation data regarding cleaning, disinfection, and sterilization for certain reusable devices, such as duodenoscopes. In June, as required by the Cures Act, FDA published a list of reusable devices for which the requirement applies, and we believe this will ensure that the premarket requirements for these device types are clear and predictable, facilitating more efficient review of these 510(k)'s and safer products for patients.

### **Least Burdensome Device Review**

The Cures Act also expands the least burdensome provisions for device review and requires important least burdensome training for review staff. In fact, even though the Cures Act mandated training only for employees involved in premarket device review, both CBER and CDRH require all medical device review staff to complete least burdensome training because it is integral to how we conduct business. When applied correctly, the least burdensome concept continues to help facilitate the availability of new device technologies without compromising scientific integrity in the decisionmaking process or FDA's ability to protect the public health. The least burdensome concept continues to be integrated into all device review and other device-related activities, not just select premarket activities.

The Agency also has revised our guidance concerning the proper response to deficiencies in accordance with the least burdensome principles and updated our guidance to incorporate the requirement under the Cures Act that summaries of significant decisions include how the least burdensome principles were applied. FDA also intends to issue in the coming months updated guidance on our overarching principles of the least burdensome concept. This is another instance where FDA is using the authorities under the Cures Act to achieve our objective of making the review process more efficient and ensuring that we are collecting information only when necessary and at the right time during the review process, and without compromising safety and effectiveness.

### **Patient-Focused Drug Development**

In the drug approval space, the Cures Act is facilitating more patient-centered, efficient, and faster drug and biologics development through different mechanisms. We are putting this patient-centered approach at the center of our regulatory activities, which is why we intend to set up a dedicated patient engagement staff in our Office of Medical Products and Tobacco.

The Cures Act emphasizes the need for patient engagement. It directs the Agency to provide information about how it is reviewing patient experience data in reviewing drugs and devices and issue guidance documents to facilitate the collection and review of patient-focused data for drug development. In May 2017, FDA published a 5-year plan for issuing these guidance documents.

FDA has already implemented an approach to record and track the submission and review of patient experience data. A new subsection called "Patient Experience Data" is now included in drug and biologic review documents. It will require reviewers to include a brief statement regarding patient experience data and related information if it is submitted and reviewed as part of an application.

In just a few weeks, the Agency will conduct a public workshop, titled "Patient-Focused Drug Development: Guidance 1—Collecting Comprehensive and Representative Input." The workshop is scheduled for December 18, 2017. FDA is holding this public workshop to obtain feedback from stakeholders, including patients, caregivers, patients' advocates, academic and medical researchers, expert practitioners, drug developers, and others, on considerations for: (1) standardized nomenclature and terminologies for patient-focused drug development; (2) methods to collect meaningful patient input throughout the drug development process, and (3) methodological considerations for the collection of patient data, and the reporting, management, and analysis of patient input. FDA has announced this workshop in the Federal Register and will publish a discussion document before it takes place.

### **Drug Development Tools**

Provisions designed to advance the development and use of drug development tools (DDTs) are some of the most meaningful provisions in the Cures Act. These



provisions codify FDA's role in qualifying biomarkers and other DDTs, that is, determining that a DDT can be used for a particular context of use across different product development programs. Product development tools are critical to efficient, expedited product development.

FDA is establishing a qualification process for DDTs (i.e., biomarkers, clinical outcome assessments (COAs), and animal models) for proposed contexts of use for drugs and biologics. There are similar efforts underway with respect to medical device development tools. FDA must develop a new regulatory process to qualify DDTs to facilitate timely and consistent review of DDT qualification submissions and publicly disseminate information about DDTs under review and following a qualification determination. Once a drug development tool is qualified under this new process, it can be used for its qualified context of use to support regulatory decisions regarding a drug or biologic, including decisions regarding an application for approval or licensure of a drug or biologic or to support the investigational use of a drug or biologic.

To better integrate our work on drug development tools, on August 15, 2017, CDER moved the Biomarker Qualification Program from the Office of Translational Sciences into the Immediate Office of the OND. This places the Biomarker Qualification Program in closer proximity to OND review divisions, fostering improved coordination, scientific understanding, and consistency between biomarkers developed for qualification and those under development as part of drug-specific programs. Similarly, the placement of biomarker and COA qualification programs in the OND Immediate Office enables greater efficiency of operations and greater opportunities for collaborative engagement with external stakeholder communities.

These efforts are already having an impact: the first COA from the COA Drug Development Tool Qualification program has been accepted for review under these updated provisions—the Symptoms of Major Depressive Disorder Scale—and the Agency expects to act on that submission soon. The Scale is a 16-item, patient-reported outcome instrument intended to capture the patient voice by measuring the symptoms of major depressive disorder that matter most to patients.

FDA has also been active with NIH and other stakeholders in the development of evidentiary criteria to support biomarker qualification efforts. Two recent multi-stakeholder collaborations have been held to help inform future guidance by the Agency, discussing the evidentiary criteria to support biomarker qualification efforts.

#### **Limited Population Pathway for Antibacterial and Antifungal Drugs**

The decline in antibacterial drug research and development as serious antibacterial drug resistant infections increase is a critical public health and patient care concern. FDA is working to implement the Limited Population Pathway for Antibacterial and Antifungal Drugs (Limited Population Pathway, or LPAD) provision of Cures to help address this. The Limited Population Pathway allows FDA, at an applicant's request, to approve an antibacterial or antifungal drug, alone or in combination with other drugs, as a limited population drug. This provision builds on ongoing efforts to spur drug development in this area by facilitating the development and approval of antibacterial and antifungal drugs intended to treat serious or life-threatening infections in a limited population of patients with unmet need. In certain circumstances, the Limited Population Pathway will be an important tool enabling FDA to conclude that the benefits of a drug outweigh its risks in the intended limited population.

As required in the Cures Act, FDA is in the process of developing draft guidance describing the criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial and antifungal drugs. FDA also is familiarizing the scientific and policy community involved in antibacterial drug development with the Limited Population Pathway by mentioning it during public presentations, workshops, and Advisory Committee meetings where development of antibacterial drugs for serious or life-threatening infections is discussed. Additionally, FDA is working with drug sponsors who are interested in utilizing this new pathway by answering questions and providing application-specific information to sponsors when it is requested.

#### **Susceptibility Test Interpretive Criteria**

Susceptibility testing is performed in laboratories to determine which antibacterial drugs are likely to be active against the bacteria causing a patient's infection. This information helps healthcare providers to pick an appropriate drug to treat a patient's infection or to determine when additional infection control procedures should be put in place to reduce the chance of spread of resistant bacteria.

Before Cures, FDA had a laborious, duplicative process to keep this information up-to-date in drug labeling. FDA is currently working to implement section 3044 of the Cures Act, which clarifies the Agency's authority to efficiently update susceptibility test interpretive criteria, including by leveraging work done by standards development organizations [SDOs], while FDA retains full authority over recognition decisions, and take advantage of tools like the web to modernize how we update susceptibility test interpretive criteria. This allows sponsors of antimicrobial susceptibility testing devices to utilize this information more quickly.

On October 30, 2017, as a first step in implementing this new authority, FDA published a Federal Register notice asking for information to assist FDA in identifying SDOs that meet the statutory requirements in the Cures Act. FDA is working to meet its December statutory deadline to publish the Susceptibility Test Interpretive Criteria website. This website will include FDA's recognition, in whole or in part, of susceptibility test interpretive criteria established by SDOs. More information will be provided about the recognition process when the website is live.

### **Continuous Manufacturing**

Continuous manufacturing—a technologically advanced and automated manufacturing method—provides a faster, more reliable way to make pharmaceuticals. This can help reduce drug shortages and recalls related to problems with product or facility quality.

The Agency is helping to bring continuous manufacturing into widespread use by supporting the pharmaceutical industry's transition to this manufacturing method. With this in mind, the Cures Act allows FDA to issue grants to study continuous manufacturing of drugs and biological products and similar innovative monitoring and control techniques.

During fiscal year 2017, CDER granted an award to the University of Connecticut to develop and build a continuous manufacturing platform with modular components for complex dosage forms, as well as to create a library based on Graphical User Interfaces. These activities support quality-based risk assessment and provide a roadmap to modernize technology and solve continuous manufacturing challenges for complex dosage forms. They also can help the Agency with review processes and provide necessary information to guide policy development. This research is likely to advance the Agency's regulatory science and facilitate production of high-quality, cost-effective complex drug products for the benefit of the public.

### **Novel Clinical Trial Designs**

As technology improves, so does FDA's ability to explore novel trial designs that better fit the needs of researchers and patients. FDA is committed to supporting the use of novel trial designs, modeling, and simulations in drug development and review, to do things like support evidence of effectiveness, optimize dosing, and evaluate adverse event mechanisms.

Building on work that was already underway at the Agency, the Cures Act specifically calls on FDA to assist sponsors in incorporating complex adaptive and other novel trial designs into proposed clinical protocols and applications for new drugs and biological products to facilitate more efficient product development. To do this, FDA is actively planning a public meeting for March 20, 2018. The Agency plans to issue guidance on, among other things, how to use such novel trial designs, how they can help to satisfy the substantial evidence standard, and what are recommended analysis methodologies.

### **Combination Products**

In line with section 3038 of the Cures Act, which addresses the full life-cycle for combination products, the Agency is taking a range of actions to advance the consistency, efficiency, predictability, and transparency of both the premarket review and postmarket regulation of combination products.

FDA is committed to this work. Leadership of the medical product centers and other appropriate offices sit on the Combination Products Policy Council to guide efforts in the pre-and post-market space. For example, the Agency is currently completing a pilot of a more streamlined intercenter consult process that improves the efficiency of these consultations, an effort that has involved training for over one thousand review staff in the three medical product Centers. Additionally, we are enhancing our training of review staff, such as leveraging prior Agency determinations, to ensure a risk-based approach to regulation of combination products.

FDA is also working to help streamline the process to get these important products to patients. In January, we released final guidance on current good manufac-

turing practices for combination products, which outlines flexible practices that can be utilized by manufacturers to reduce burdens.

A key provision in the Cures Act calls for FDA's Office of Combination Products (OCP) and the three medical product Centers to work with and provide assistance to medical product sponsors upon request regarding the study design of their product. OCP continues to provide this assistance and has developed a new standard operating procedure for handling these requests to ensure faithful implementation of the Cures mandate.

### Real World Data and Real World Evidence

Advances in technology also have the potential to improve the availability and utility of real world evidence (RWE) and real world data (RWD). The Cures Act specifically supports the Agency's evaluation of the potential use of RWE to support the approval of new indications of approved medical products or to satisfy post-approval study requirements for marketed products.

Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in-home use settings, and data gathered from other sources such as mobile devices that can provide information about health status. RWD sources (e.g., registries, EHRs, and administrative and healthcare claims data bases) can be used as a data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

The use of RWE and RWD have the potential to allow researchers to answer questions about treatment effects and outcomes more efficiently, saving time and money while yielding answers relevant to broader populations of patients than might be possible in a specialized research environment. This could help streamline clinical development. The use of these data also can help inform the safe and effective use of medical products.

To do this, FDA will establish a program to evaluate the potential use of RWE to help support the approval of a new indication for an already approved drug or to help support or satisfy post-approval study requirements. Over the past year, CDRH, CBER, and CDER have harmonized their definitions for RWD, data relating to patient health status and the delivery of health care routinely collected from a variety of sources, the clinical evidence regarding the usage, and potential benefits or risks of a medical product derived from analysis of RWD. FDA has already finalized guidance on RWE for devices, and we will issue new guidance to define how we plan to incorporate these principles into product development for drugs and biologics.

FDA's focus on RWE has already advanced patient care. On June 5, 2017, FDA became the first regulatory body in the world to approve the most recent iteration of the Sapien valve, the Sapien 3, to treat high-risk patients whose surgically placed aortic or mitral bioprosthetic valves were old and worn out. This approval was based in part on data from the Transcatheter Valve Therapy (TVT) Registry, a partnership of the American College of Cardiology and the Society of Thoracic Surgeons. The TVT registry collects clinical data on the performance of transcatheter valve replacement procedures performed in the U.S. once a product goes to market—including both on-label and off-label uses—making it possible, under certain circumstances, to accumulate more data faster, without the need for costly and time-consuming formal clinical trials.

FDA is currently focused on developing a framework for a program that will evaluate the use of real world evidence to support regulatory decisions for new indications or post-approval study requirements. The draft framework, required under the Cures Act, is due in December 2018, but the Agency is already gathering stakeholder input to move this field forward. For example, in September 2017, FDA collaborated on a workshop convened by Duke-Margolis Center for Health Policy to bring stakeholders, including industry, academia, and patient advocacy groups, together to discuss both the challenges and opportunities for applying RWE and RWD to drug development. Similarly, the National Academies of Sciences, Engineering, and Medicine have organized a series of meetings—with FDA participation—to explore these opportunities. The first, also held in September 2017, was entitled "Examining the Impact of Real-World Evidence on Medical Product Development: A Workshop Series." Two additional meetings are planned.

FDA also is supporting numerous demonstration projects to advance the regulatory framework for how best to incorporate RWE into regulatory decisionmaking. For example, as part of a big data analytics initiative at the FDA called Information

Exchange and Data Transformation (INFORMED), the OCE has a current collaboration with Flatiron Health to examine how RWD can be used to gain insights into the safety and effectiveness of new cancer therapies.

In addition, in June 2017, FDA announced a partnership with CancerLinQ, the American Society of Clinical Oncology's big data initiative. FDA and CancerLinQ will be using real world, aggregate, de-identified patient care data from oncology practices to understand a variety of issues related to the appropriate use of newly approved therapies. The initial focus will be on immunotherapy agents approved for melanoma. FDA is also leading an effort that includes NIH's National Center for Advancing Translational Sciences, National Cancer Institute, National Library of Medicine, and the HHS Office of the National Coordinator for Health Information Technology to develop a general framework by harmonizing several Common Data Models.

FDA will continue to partner with a range of stakeholders to do all the Agency can to address the challenges and realize the opportunities posed by RWE and RWD, so that FDA can get effective treatments and therapies to those who need them more efficiently.

### **Medical Countermeasures**

At FDA, we remain fully committed to continuing to use our authorities to the fullest extent to help facilitate the development and availability of medical countermeasures—such as vaccines, therapies, and diagnostic tests—to counter chemical, biological, radiological, nuclear (CBRN) and emerging threats such as pandemic influenza and Zika virus.

While many of the provisions in the Cures Act that are intended to facilitate the development and availability of medical products in general also will serve to help facilitate the development and availability of medical countermeasures, the Cures Act contains two FDA-specific provisions to help advance the development and availability of medical countermeasures.

Section 3088 of the Cures Act amends FDA's Emergency Use Authorization (EUA) authority (section 564 of the FD&C Act) to permit EUAs that: (1) authorize emergency use of unapproved animal drugs or unapproved uses of approved animal drugs, (2) make applicable other emergency use authorities (e.g., to issue emergency dispensing orders, waive compliance with Current Good Manufacturing Practices, make available CDC Emergency Use Instructions, and extend expiration dates) to approved animal drugs, and (3) allow unapproved animal drugs to be held for emergency use. In January 2017, FDA issued guidance on Emergency Use Authorization of Medical Products and Related Authorities, in which we explained that the Emergency Use authorities and guidance recommendations are now applicable to animal drugs and encouraged anyone interested in utilizing these authorities to contact FDA to discuss how to proceed. FDA plans to address any issues raised as we develop more experience with these new authorities.

Section 3086 of the Cures Act adds section 565A of the FD&C Act for FDA to establish a new priority review voucher (PRV) program to help incentivize the development of material threat medical countermeasures. Upon approval of a material threat medical countermeasure application, FDA will award a PRV provided certain criteria are met. The PRV may in turn be used by the sponsor who receives it, or sold to another sponsor who may then use it, to obtain priority review for a product application that would otherwise not receive priority review. In October 2017, we announced in the Federal Register the fee rate for using a material threat MCM PRV for fiscal year 2018 (\$2,830,579; the rate was effective on October 1, 2017, through September 30, 2018). We also plan to issue guidance to address medical countermeasure-specific issues in the near future, with the intent to implement the program consistently with the other PRV programs, such as the Neglected Tropical Disease Voucher Program.

The FDA stands ready to use these new authorities as appropriate to help facilitate the development and availability of medical countermeasures.

### **Conclusion**

These are just some of the ways the Cures Act has supported and enhanced FDA's work to make the process for bringing safe, effective, and innovative treatments to patients more efficient. FDA's improvements in transparency, consistency, predictability, and efficiency will benefit industry, healthcare providers, and, most importantly, patients. We expect our continued implementation of the Cures Act will further advance these goals. The Agency stands ready to work with Congress and stakeholders to help make the promise of the Cures Act a reality.

Thank you for inviting FDA to testify today. I would be happy to answer any questions you may have.

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The CHAIRMAN. Thank you, Dr. Gottlieb.

We'll now begin a round of 5-minute questions. In my 5 minutes, I have several questions, so let me go through them pretty quickly.

Both of you have talked about regenerative medicine. Your testimony has more about it. There are a number of Senators, including the majority leader, who are very interested in it, and it helps if we're trying to get more money and more legislation to have his continued interest.

Would each of you, in the next few weeks, send to me and to Senator Murray a brief written report summarizing what you've done in the area of regenerative medicine, the kind of thing that I mentioned that helped Doug Oliver, both about how you create more hope for people like Doug, but also what you're doing about the bad actors in the field? I'd like for it to be the kind of memo I could give to other Senators who are interested in this to show that you've taken some action in the first year.

Dr. GOTTLIEB. Absolutely.

Dr. COLLINS. Yes.

The CHAIRMAN. Thank you for that.

[The following information can be found on page 13 and 18 in the appendix:]

The CHAIRMAN. Dr. Collins, could you say in about 30 or 45 seconds what you mean when you say Other Transactions Authority has been helpful to you and you'd like to have more of it?

Dr. COLLINS. Other Transactions Authority allows us to move very flexibly in an area of high need and where technology is advancing rapidly. It means that we can bring partners together without taking the whole year that it often takes to issue an opportunity for grants to be submitted and for us to do the reviews and make the awards, plus it gives us the flexibility to decide when a particular partner is not meeting milestones and we can just cut them off without any further to do. This is something that DARPA has used. We are delighted to have that for our common fund and for All of Us, the Precision Medicine. It makes things possible much faster.

The CHAIRMAN. Where do you want it that you don't have it?

Dr. COLLINS. We could really use this now in the opioid crisis. We have a big plan that we want to move forward quickly. This would be a great advantage to have as one of the tools.

The CHAIRMAN. Senator Murray and Senator Blunt in their Appropriations Committee, I believe, have for the third consecutive year reported out a \$2 billion increase in NIH funding. Can you summarize in less than a minute why you believe that as we appropriate money for opioids that some of that money ought to go for research into non-addictive pain medicines?

Dr. COLLINS. The critical solution for the future is to have alternatives for opioids for people who suffer from chronic pain, and there are 25 million of them in the United States right now that have pain every day. We need to have better alternatives. There are ways to get there with some exciting new drug targets that have emerged. Working with industry, with a lot of contributions

from NIH, we believe we can accelerate that process, particularly with OTA to help us, and to be able then to have available for those people who have that kind of pain answers and much more—

The CHAIRMAN. You're talking about using additional appropriations and additional private money in a public-private partnership to accelerate that. Correct?

Dr. COLLINS. Exactly, and we would expect companies to be willing to put some of their funds into this, too, just as we've done with other partnerships on Alzheimer's Disease, diabetes, rheumatoid arthritis, and Parkinson's.

The CHAIRMAN. Finally, Dr. Gottlieb and Dr. Collins, but I'll start with Dr. Gottlieb, it takes sometimes 10 or 12 years to take a breathtaking new medical innovation from idea to the doctor's office. The whole goal of Cures is to shorten that period and shorten that cost and still do it in a way that's safe and effective. What are you doing—can you give me some specific examples of how FDA and NIH and CMS, which has to do with funding, are working together so that we don't make a lot of progress in research, for example, have it sit on the shelf while FDA works on something else, or make a lot of progress at the FDA and have it sit on the shelf while CMS is deciding whether to fund it?

Dr. Gottlieb.

Dr. GOTTLIEB. I think a lot of our ability—and thank you for the question, Senator. A lot of our ability to make the development process itself more efficient and lower cost is trying to develop better tools, better scientific tools to evaluate products that are being brought through the development process to ascertain their safety and effectiveness in more efficient ways, in ways that are faster, that can be done at a lower cost. That is a process of developing better science, better regulatory science for evaluating technology.

There's a lot of work that we're doing in concert with the NIH in collaboration with Dr. Francis. A couple of initiatives I'd point out to you are the tissue on a chip initiative, which is an initiative for developing better tools for toxicology and looking at issues of safety and effectiveness, and a Partnership for Accelerating Cures, which is another collaboration where we are developing these tools.

I'll just close by saying I think that if we can develop this better science, this is a case where we could have the best of both worlds, a process that's lower cost and more efficient, but also is going to give us a better measure of safety and effectiveness, the ability to determine those parameters.

The CHAIRMAN. Well, I'm out of time. But as we continue our oversight—and I'm sure you're going to do this—we need to think of this as a seamless process, and we need to go from idea to the doctor's office to the patient, and we need to get it through the research into the FDA, through CMS, to make these things work, and I hope you'll pay a great deal of attention to that.

Senator Murray.

Senator MURRAY. Thank you very much.

Dr. Gottlieb, let me start with you. As you know, we had some deadly outbreaks of antibiotic-resistant infections that were linked to contaminated duodenoscopes in my home state and actually across the country, and I championed a provision in the 21st Cen-

tury Cures that provided FDA with some additional tools to make sure of the safety of reprocessed medical devices. I really appreciated the FDA meeting its guidelines to publish the list of devices for which the agency now requires valid evidence-based cleaning procedures.

Can you update us on how many products now have these validated cleaning protocols because of this law?

Dr. GOTTLIEB. Thank you, Senator, and I'll just preface my answer by saying we think that this is a very important authority and plan to make robust use of it, and as you mentioned, we put in place the provisions in August 2017. There have now been 14 products, I believe, to date that have gone through the 510(k) process outlined in this legislation. We have many more that we're having discussions with, and I can get you a fully up to date number because it's evolving. But it's about 14.

Senator MURRAY. Okay, great. I really appreciate it, and I want to stay updated on this because I think we do need to respond quickly and appropriately when problems occur with these medical devices. So patients need to trust what's being used, so I really appreciate that.

Dr. Collins, I was very proud to champion provisions in the Cures Act to improve the inclusion of historically underrepresented populations, as I mentioned—women, racial and ethnic minorities, children, seniors—into clinical research. One of the provisions was a task force to improve the evaluation of drugs for pregnant and lactating women. They are in a very difficult position often today, whether it's treating morning sickness or a chronic condition, because there's so little research today on how medication might impact them. We all know if they don't get an answer from the doctor, they go online, and that just, to me, is unacceptable in today's world.

How do you plan to integrate the task force work into the broader efforts to advance innovation and impact clinical research?

Dr. COLLINS. Thank you for the question. We welcomed that recommendation in the legislation, and we've moved swiftly to set up this group, the PRGLAC, chaired by Dr. Cathy Spong, who is a very respected neonatologist and OBGYN expert at NIH. That group has already met twice and is going to meet again twice more in the next coming months, and by May 2018, we'll have a series of recommendations, which we intend to take with great seriousness.

As you understand very clearly, this is an issue where we want to be sure that we are carrying out the appropriate clinical trials to understand about efficacy and safety during pregnancy and lactation. But we also know those are very sensitive times in terms of not creating risks, and so getting the balance just right is what this Committee is wrestling with. It's a strong group. They've gotten very quickly engaged. I think you're going to see something very substantial come out of this.

Senator MURRAY. Good. Well, I'm hearing from a lot of women who are very concerned about the direction our country is going today, whether it's family planning or allowing employers to deny access to birth control. So they are looking for good information.

I know that one of the things we did in Cures was to strike a real balance between members of the Federal Government and external stakeholders on the task force. Today, the non-Federal members have not been hired by the task force and haven't been able to fully participate. I wanted to ask you how you are ensuring that the nongovernmental voices that Congress required to be included in this are heard from and they are incorporated fully into this.

Dr. COLLINS. We very much want those voices to be critical. They're probably the most critical parts of this. They have been attending all of the meetings and are speaking. The problem is getting them officially appointed, which means going through the ethics clearances. I am assured that by the February meeting, they will all have gone through that process and will be fully installed and able to actually not just be present but also to vote.

Senator MURRAY. Well, that's really important. Can you keep me updated on that? I'd like to make sure that's implemented.

Dr. COLLINS. I'd be happy to.

Senator MURRAY. Dr. Gottlieb, I just wanted to ask you—I've just got a few seconds left. But we're living in a new digital age. It's been mentioned several times. Some of the products are low-risk. Some of them have a big impact on patients and their safety. People are wearing wearables. We're seeing a lot of different things, apps that use camera phones to diagnose diseases. These are really promising, but we have to make sure they work and their claims are backed up by hard evidence.

I know the agency is working to speed that up right now. But, to me, it's less clear how FDA is going to ensure that the sheer quantity of products that are now on the market are being validated. I wanted to ask you what actions FDA is taking to make sure that patients and providers can put their trust in the digital health products.

Dr. GOTTLIEB. I'll just quickly, Senator—and thanks for the question. We continue to receive adverse event reports even for software products and digital products that we might exclude from regulation based on the parameters outlined in the Cures statute. If there was a situation where we received an adverse event report that led to a recall of a product, even a product that we had excluded from regulation, that would be a reason for us to then bring that product back under regulation through the provisions in Cures, because if some adverse event or some issue with the software itself is leading to an adverse event, that tells us that it shouldn't have been excluded in the first place. So we continue to monitor even the products that we're scoping out of our active regulation.

Senator MURRAY. Okay. We want to stay updated. That's going to take a lot of work in the future.

Thank you.

The CHAIRMAN. Thank you, Senator Murray.

Senator Roberts and Senator Young have deferred to Senator Cassidy.

Senator Cassidy, we have our hearing next Wednesday on oversight of mental health law that you and Senator Murphy worked on, so that will be here.

Senator CASSIDY. Wonderful. I thank my colleagues for allowing me to go. I'm supposed to be at the White House, so I thank you.



This is not an Appropriations Committee, but it's a broad topic, and so if you don't mind—Dr. Collins, again, great respect for you and for your institutes. But as I have pointed out in the past, we don't seem to have an NIH which targets funding relative to disease burden. So when I look at NIDA, their budget only went up 2 percent last year, and it still remains far smaller than other institutes in which there is far less morbidity and mortality flowing from those disease conditions.

If we are going to address the issues of opioids or mental health, both of which are playing into this, it seems like there has to be a greater shift in where our funding is going at NIH toward these disease conditions. Now, in the past, you've suggested that, well, we'll kind of organically grow—hold this one stable and allow this one to grow—but when I look at it, all the institutes seem to be growing at about the same pace.

I guess my question for you is it doesn't seem as if NIH is making these a priority if you look—over other conditions if you look at the relative funding increase of those institutes. You're a very thoughtful person. So please give me your thoughts on that.

Dr. COLLINS. Senator, you point to a very important issue about how do we make decisions. I have to point out, however, that it's the Congress that assigns a budget. It's a line item every year in the appropriations process to each of those institutes. As the NIH director, I don't get to set those numbers, and so we follow what the Congress tells us ought to be the appropriation for a given year.

Then we work with great flexibility to try to be sure that when there is a public health need, as there is now—for instance, with opioids, which I think you're referring to—because, of course, we have a big opportunity there in terms of our understanding of how the brain works, the BRAIN Initiative is directly relevant here, and the Neurology Institute has an enormous investment in understanding pain, as does the National Center for Complementary and Integrative Health.

One shouldn't look at our organizational structure and say that the money actually fits precisely into those buckets. We have lots of ways that we can mix and—

Senator CASSIDY. I accept that, if I may, just because I have limited time. So you're saying that if we want more money to go to the National Institute of Drug Addiction, we need to line item it in our budget.

Dr. COLLINS. That's the only way it happens.

Senator CASSIDY. That said, the flexibility does seem as if it should be flexing toward things like NIDA. Pain is important, but, ultimately, pain translates into addiction. That's a final common pathway. So it does seem as if we should be flexing toward them. Is that where the flexing is taking place?

Dr. COLLINS. I think that's what we're trying to do, is to shift with the priority opportunities we have more funds into that space, because we recognize this is a terrible public health emergency.

Senator CASSIDY. Let me ask on this, a different topic, again, trying to stay on time. There is a move afoot to suggest that marijuana usage can be used in lieu of opioids, that states that have

legalized marijuana more liberally have lower incidents of opioid addiction.

Dr. COLLINS. That's right.

Senator CASSIDY. But then I read about the brain being pretty plastic up until age 25, and so—and we all know the pothead, the kid that has Amotivational syndrome, if you will. So there's been at least one suggestion I've read that we should make a recommendation that legalization of marijuana should be restricted to those 25 and above. I say this not because I'm an expert but to get the thoughts of those such as the two of you who are experts.

Dr. COLLINS. Well, there is published data, although it's still controversial, that heavy use of marijuana beginning in adolescence does have permanent consequences in terms of intellectual performance, that IQ points get lost in those individuals who have been exposed a lot to marijuana starting in adolescence. It is also true, as you said, that there seems to be a statistical relationship between the states that have legalized marijuana and a reduced incidence of opioid overdoses and deaths. But one has to be careful there. That's a correlation and not necessarily a causation. I would not want to leap to that.

I would just go, though, to the point that we are increasingly studying the cannabinoid receptor pathway in the brain as a potential way that we might come up with alternatives that would be effective for managing pain and depression and anxiety—not marijuana itself, but using that pathway.

Senator CASSIDY. I accept that. But for the two of you, is it a reasonable public policy consideration that perhaps the age of legal marijuana for those states that are legalizing should be 25 and above?

Dr. COLLINS. We're getting into difficult public policy territory. I will simply say the concerns about marijuana exposure to the developing brain would have to be strongly considered in anything that made access to adolescents more readily available, because we do have that concern.

Senator CASSIDY. The brain is developing at least through age 25.

Dr. COLLINS. You could say 22. You could say 25. I don't know that I have a precise dividing line.

Senator CASSIDY. My wife says it's 60, but that's—you know.

[Laughter.]

Senator CASSIDY. Dr. Gottlieb? I'm out of time. I'm sorry. I should yield back. I apologize. Thank you.

The CHAIRMAN. Thank you, Senator Cassidy.

Senator Casey.

Senator CASEY. Mr. Chairman, thank you very much. I do want to add my words of commendation to you and to the Ranking Member for the work you did to get this legislation passed. It is hard to believe that it's been a year, and I know we have a ways to go with regard to implementation. But in a place and in an institution where there aren't many days where you have not just bipartisanship but bipartisanship that undergirds a substantial matter of public policy of this importance, it's especially great to be able to celebrate this passage and to continue to work together.

Dr. Gottlieb, I wanted to start with you on a question regarding 503B compounders. While we've primarily been focused in the hearing on getting new drugs to patients, I'm also concerned about maintaining the supply of drugs already in the market. We know that since Hurricane Maria hit Puerto Rico, I've heard from Pennsylvania hospitals regarding a shortage of IV fluid and amino acids for injection, a critical product for patients who must receive nutrients intravenously.

While Puerto Rico is 1,500 miles away, providers in Pennsylvania now face product shortages due to challenges facing major medical product manufacturing facilities located on the island. The shortages are especially damaging, because in the case of the IV fluid and amino acids, the facilities on the island were the sole source of the product for the entire country. So when you mentioned continuous manufacturing and how that can help reduce drug shortages, I wanted to ask you: Could 503B outsourcing facilities also help in the case of drug shortages?

Dr. GOTTLIEB. The short answer is yes, Senator. We remain extremely concerned about the shortage situation in Puerto Rico, particularly as it relates to the IV fluids you referenced and the amino acids. We think that the steps we've taken in concert with the manufacturers and the authorities in Puerto Rico was thought to alleviate the shortage situation going into next year. But we still have to get through December, and we still face another hard month where there's going to be challenges getting access to an adequate supply. But we do expect this to continue to improve going forward.

The issue with the 503B compounders—they theoretically can compound this product. They would have authority to do that. One of the issues is that the products that are in shortage aren't just the IV solutions themselves but the actual physical plastic bags to put the IV solutions in. So the 503B compounders also face a challenge getting access to the plastic bags that they need in order to compound the product, because those were also manufactured in Puerto Rico. So that has been a challenge, and whereas you would have expected the 503B facilities to be able to step in to supply more of this market, I think that they've been limited in their ability to do that.

Senator CASEY. I wanted to ask you as well—and I know we have limited time—but with regard to the Pediatric Priority Review Voucher Program, we know that an estimated one in 10 people in the United States, two-thirds of whom are children, have a rare disease, according to the National Organization for Rare Disorders. Despite the need, private companies are less likely to pursue new therapies for rare diseases because it requires making an investment in products that will likely not re-coup the high costs associated with their research, development, marketing, and distribution.

As you will remember, I worked with Senator Isakson, Chairman Alexander, and Ranking Member Murray to extend this review program at FDA, and this particular program provides important incentives to companies to invest in new therapies for rare pediatric diseases. When we last spoke, the FDA was still working on implementing changes that were made to the program, most importantly

the definition of what constitutes, quote, “rare pediatric disease,” unquote.

Can you give us a sense of the progress that you’ve made on the update of that definition, and are you meeting the statutory requirements to respond to requests for companies seeking designation for their products within 60 days? I know that’s a lot.

Dr. GOTTLIEB. I’m proud to say we are, Senator, and we have put forward some guidance. I think there’s some additional guidance coming out on implementing the PRV Program. You know, we continue to look at this as a potential opportunity. We’re awaiting the GAO report, as are others, to better evaluate these. I would just close by saying I think that there’s a lot of other things that we can and are doing to try to create additional efficiencies to address some of the challenges that you outline with respect to pediatric drug development, including one we took yesterday. So I just want to put a plug in for a policy we put out yesterday trying to outline a more efficient clinical development pathway for drugs targeted to very rare pediatric diseases.

Senator CASEY. Thanks, Doctor.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Casey.

Senator Young.

Senator YOUNG. Doctors Collins and Gottlieb, I have a lot to cover in 5 minutes, so I ask that you try and be concise with these questions. So thank you for your presence here today.

Dr. Collins, you mentioned in your testimony the plans you have in implementing the Eureka competitions for a vision in Cures, that prize program. When I was in the House of Representatives, I put together an amendment to Cures. A variant of this became the Eureka prize provision. I know some others contributed to that effort as well. It was inspired by a neighbor of mine who is a latter day Thomas Edison. He develops medical devices in his garage.

I consulted with eminent economists, healthcare professionals, researchers, venture capitalists, angel investors, and all sorts of individuals in developing my form of prize. The objective was to ensure that we have objective rather than highly subjective criteria with respect to what those prizes are offered for. My hope—something articulated by one of my colleagues here today—was that we would target funding according to disease burden.

When my colleagues consulted with the NIH, they were told, no, they don’t want to be directed. So it effectively killed this effort, which I, frankly, find more meritorious than the current provision.

What criteria do you or others within NIH use to determine what areas you’re going to be funding, with due acknowledgement that we’re funding Alzheimer’s now? That strikes me as meritorious, on first blush. But what criteria do you use?

Dr. COLLINS. I appreciate the question. By the way, at every Senator’s place, this booklet which is published this week will walk you through a lot of the responses to that. How do we decide where the priorities are? Certainly, disease burden is a huge part of that. Let me be very clear about that. At the same time, scientific opportunities don’t always happen at the same pace in the same areas, and when you see an opportunity that’s particularly ripe for investment, we don’t want to miss that.

With the prize mechanism, we just put out a request for ideas about prizes for Alzheimer's Disease—talk about an area of high disease burden. We're looking forward to seeing what that will look like. We have a prize right now that's waiting for responses—and it's stirring up a lot of interest—in antimicrobial resistance, coming up with a test that will tell you within 4 hours—

Senator YOUNG. All the criteria are located in that book you just held up? Is that the case?

Dr. COLLINS. It will go through quite a lot of it. If you need more information, I can supply it.

Senator YOUNG. Okay. I'll be scrutinizing that, and I thank you for that, for publishing that information. Do you include or do you plan on including the private sector or outside stakeholders, like some of those I mentioned, as we move forward in reviewing proposals and in designing prize competitions?

Dr. COLLINS. Absolutely. Yes in both cases. Our review panels, especially for high-technology efforts—we populate those with people from the private sector who have that expertise. Certainly, in prize competitions, right now we want to see what people think in all sectors about an Alzheimer's prize.

Senator YOUNG. Last, do you allow in your prize competitions or have any plans to offer in-kind benefits? By that, I mean the ability for a garage investor or a researcher to use lab space at the NIH, or to use equipment that we, the taxpayers, have paid for, or to offer technical assistance to those that need it?

Dr. COLLINS. Yes. I think we've done that, and, actually, in a couple of the small project prizes where we're particularly asking students, undergraduates, who have a great idea, to be able to apply, and they may not have access to the equipment, we are trying to be very flexible on that.

Senator YOUNG. Well, thank you. It sounds as though the career NIH folks that were telling Members of Congress that our idea was not thought well enough perhaps were on the right track.

Dr. Gottlieb, pharmaceutical development today frequently involves what's been called shooting in the dark, making key decisions that impact a development program's success with very limited data. For example, decisions including indication selection, dosage endpoints, and inclusion-exclusion criteria, you might say are made sub-optimally because the data that informs such decisions lies in inaccessible siloes, at least inaccessible to most stakeholders. This contributes significantly to higher R and D costs and longer timelines. Now, the FDA already has much of this data, this otherwise siloed information.

My question for you is: Has the FDA taken any steps in aggregating healthcare data across siloes to improve the pharmaceutical development process? If not, would the FDA be willing to analyze the data it collects to provide further scientific insight back to the research community to accelerate and de-risk biomedical innovation?

Dr. GOTTLIEB. I appreciate the question, Senator. It's a complex one, and I'd be delighted to follow-up with you on it. But the bottom line is that there are situations—first of all, we're going to be taking some steps very soon to make more data from the clinical portion of the review from approved applications public where they

can be aggregated into the kinds of datasets that you speak of. There are situations where we develop our own proprietary datasets from data that we glean across applications to make decisions, particularly around drug safety. But those datasets remain proprietary to the FDA because that information is commercially confidential.

We are looking at how we could make these datasets public in a de-identified way without appropriating anyone's intellectual property around their own data, because my belief is if we're making regulatory decisions on the basis of aggregated data that isn't accessible to the public, that's probably something we should try to address. So this is a very complex area that we're actively working on. It'll suffice to say we are trying to move in the direction that you suggest. There are legal complexities associated with it.

The CHAIRMAN. We're out of time. Maybe you could—

Senator YOUNG. I look forward to working with you.

The CHAIRMAN. Thank you, Senator Young.

Senator Bennet.

Senator BENNET. Thank you, Mr. Chairman. I want to also congratulate you and Senator Murray on this 1 year anniversary—one more reason to be happy to be on this Committee.

Dr. Gottlieb, I just wondered if you could give the Committee a little bit of an update on where you are with the implementation of the Med Tech Act, the bill that Senator Hatch and I worked on together.

Dr. GOTTLIEB. Well, I appreciate the question, and I'll try to be brief. We just announced major components of implementation of some of those provisions today. So we continue to move forward with this on schedule. I think that it's a good example of what we're trying to do in this space. It's a good example of what we're trying to do generally with Cures, where we're taking the provisions that Congress outlined and trying to take the spirit of what Congress set out to achieve and trying to go beyond that.

For example, Congress set out to create a more efficient process for the review or to exclude certain decision support tools used by clinicians. In the announcement we made today, we're also going to exclude certain decision support tools, digital tools that are used by patients as well as—as long as they meet certain parameters, and that's an attempt by FDA to try to take the spirit of what Congress set out to do and extend it a little bit.

Senator BENNET. What sorts of things do you expect to see sort of sooner rather than later in terms of new devices for patients?

Dr. GOTTLIEB. I think one area of development that we haven't seen as much of is in the area of decision support tools, where there's tools that could take information and help support decisions without making a decision for the clinician or the patient. I think, in part, there's a lot of reasons why we haven't seen as much innovation in that space as you would have thought, but regulatory ambiguity probably played a role for a period of time.

FDA always intended to exercise enforcement discretion in this space. Congress expressly outlined that in Cures, and so this provides us the opportunity to put out guidance that creates some really bright lines and some parameters around what does and doesn't cross the line and what are the obligations of sponsors,

even those who are excluded from active regulation, to make sure we're continuing to look at the safety of those products or collect information where things can go wrong.

I am hopeful that we're going to see more innovation in this space, tools that could sit on top of the electronic health records, for example, and help physicians make decisions from that information.

Senator BENNET. I appreciate your focus on it. I also noticed, unrelated to that, that the FDA approved the first breakthrough designated diagnostic test to detect genetic mutations for cancer. That was an approval that came through, I think, the new breakthrough therapies—or not breakthrough therapies, but breakthrough device section that we wrote for the bill—in the bill last year. I was interested to see that at the same time that happened, there was a simultaneous decision by CMS to also cover the diagnostic test.

I wonder if you could share with the Committee how you and CMS conducted these parallel reviews and whether we can expect to see this sort of coordination in the future.

Dr. GOTTLIEB. Well, I think you can, Senator, and this is an example of a test that was a laboratory developed test that voluntarily came through the regulatory process. We were able to review it in 6 months under the breakthrough designation—the first, as you said, breakthrough designated product to receive FDA approval—and we worked with CMS to have in place simultaneous coverage at the same time.

We think going forward this is a panel of cancer markers that will help guide the treatment of cancer patients and help guide the prescription of therapy. This is an area of a lot of innovation right now, and what CMS said in their policy—and I'll let them articulate it more clearly—is that panels that come through FDA for voluntary approval now will automatically receive coverage, a national coverage determination. So it's a powerful incentive, I believe, for more such tests to try to come through the regulatory process, and we can provide, I hope, a greater assurance of the effectiveness of it.

Senator BENNET. I think that's a big step forward, and I can tell Dr. Collins agrees. So thank you.

Dr. Gottlieb, the last question I have—and I only have a minute left. Senator Rubio and I last year worked on the RACE Act for pediatric cancers, and I know you guys put out some guidance recently on developing drugs in rare pediatric diseases. I wonder if you could expand a little bit about that.

Dr. GOTTLIEB. We did, Senator, and we're going to have more to say on this area. But what we did yesterday was finalize some parameters and some guidance that we had in draft form that tries to look at very rare pediatric cancer, so this is—pediatric diseases, excuse me, mucopolysaccharide diseases—trying to outline a more efficient process for developing those products. We might not have to rely as much on placebo trials and might be able to use modeling assimilation to represent the experience of the placebo arm and also allow sponsors to collaborate to try to test multiple drugs in the same clinical trial.

The reason why these kinds of accommodations, I think, are important in this setting is because it's very hard to enroll patients

in these very rare diseases where you literally might have just dozens of patients who have a disease who are eligible to be enrolled in clinical trials. Tying to allow sponsors to collaborate and look at ways where you don't have to randomize some of those patients to placebo can facilitate more efficient development.

Senator BENNET. Mr. Chairman, I'm out of time, but I didn't thank the witnesses for their great service to this country, and I deeply appreciate it.

The CHAIRMAN. Thank you, Senator Bennet.

Senator Collins.

Senator COLLINS. Thank you, Mr. Chairman.

Dr. Collins, I'm always glad to see you, and I still claim you as my cousin regardless of the facts.

[Laughter.]

Dr. COLLINS. I accept.

Senator COLLINS. Thank you. The State of Maine is doing some really exciting medical research, and I have visited a lot of the labs and medical institutes that we have in our state. The Maine Medical Center Research Institute is conducting cutting edge work that researchers in Maine have underway to develop medical treatments for chronic diseases. In September, one of the researchers with whom I met, Dr. Leif Oxburgh, and his team at Maine Medical Center received an award through the NIH Regenerative Medicine Innovation Project. Using adult stem cells, Dr. Oxburgh is working to develop novel therapies for chronic kidney disease, which is very exciting.

Regenerative medicine also holds great potential for understanding aging and reversing diseases like macular degeneration. I understand that the Chairman has already introduced Doug Oliver. But he, too, is from the State of Maine and grew up only 11 miles from where I did, and he shared his compelling story about losing and regaining his sight through regenerative therapy.

MDI Biological Laboratory in Maine is leading the development of such therapies that hold significant potential for slowing the changes that occur with aging and the diseases of aging. What especially can we do to support research into biological aging?

Dr. COLLINS. What a great question, and thank you for pointing out a number of the applications to regenerative medicine. As we are gathered here this morning, there's an intense discussion going on at a hotel in Bethesda sponsored by FDA and NIH jointly on this topic of regenerative medicine, with several hundred people in the room, talking about applications to kidney disease, to heart disease, to aging, to such things as rare diseases, common diseases, the whole landscape, and it is enormously exciting to see how that's talking place. When I spoke yesterday, I even forecasted if we do this in the way that I think we could, we could cure, not just treat, but cure a disease like sickle cell in the course of the next 5 years.

With regard to the question about aging, we are learning a lot about what that process is. I'll just mention one example—otherwise, I'll go into a long lecture—and that is that as you age, there's a certain category of cells that are no longer able to keep going. They become senescent, but they don't completely exit the stage. They're still there, and it turns out that they're not good actors.



They're actually making the healthy cells around them not so healthy.

If we could figure out, as we've already done in mice, how those senescent cells could basically be told, "Okay, you're done now," it could very significantly slow down the normal process of aging with all that that entails in terms of frailty and chronic disease. This is a pretty exciting new development.

Senator COLLINS. I think it is, also, and I remember visiting Harvard University and talking with researchers there about Alzheimer's Disease, and they're also looking at the possibility of turning proteins back on to restore cells that have been lost and neurons that have been lost.

Dr. COLLINS. Enormous excitement about all of those alternatives, as well as identifying drug targets that we just didn't know about before by very careful systems biology approaches to understanding how networks in the brain work in normal individuals and those who are at risk for Alzheimer's. We have a partnership with industry that you may have heard about called the Accelerating Medicines Partnership, which is advancing this at a pace that I wouldn't have thought possible a couple of years ago.

Senator COLLINS. That brings me to my question for you about that program. Which aspects of the Accelerating Medicines projects do you find most promising?

Dr. COLLINS. Well, for Alzheimer's, there are two areas that we're really pushing. One is biomarkers. We really need to find out what are the indications that a therapy is working without having to wait 10 years to find out whether it was, in fact, protective against the development of cognitive decline, and there's a lot going on there with various types of imaging for tau, for instance, one of those proteins that's involved in this.

The other part is this systems biology, where we're really trying to step away from what we know already and ask the question: What else is going on in the Alzheimer's brain, and how could we use that to develop this next-generation of therapeutics, taking advantage of all of the areas that we are now learning about to come up with interventions that are going to work, and then apply those early before people have already begun to succumb to the illness? We've got to start early if we want to get a good effective.

Senator COLLINS. Thank you very much, Mr. Chairman.

Thank you, Dr. Collins.

The CHAIRMAN. Thank you, Senator Collins.

Senator Murphy.

Senator MURPHY. Thank you very much, Mr. Chairman.

Thank you both for your service. I know it comes at a great sacrifice, and, particularly, Dr. Gottlieb is a Connecticut resident. I know the sacrifice that you make to serve our country. Thank you to both of you.

Dr. Collins, I wanted to talk to you a little bit more about the All of Us Research Program. This is a program that designs to build a diverse biomedical dataset for the Precision Medicine Initiative. I'm interested in it because one of the participating health centers, community health centers, that is currently gathering data is based in Middletown, Connecticut. I think it's great that you've gone out and worked with community health centers, because these

centers—you typically serve a patient population that is often underserved in biomedical research.

I just want to put that question to you, which is—if you could talk about the importance of having FQHCs as part of this initiative and whether there are plans to expand beyond the current six health centers that are right now part of this initiative. The community health center in Connecticut is very pleased with their partnership with you on this, and we'd love to see more like them get involved.

Dr. COLLINS. In my opening remarks, I put up this visual image about how it is that we are seeking to enroll participants in this very bold, largest ever prospective study of health and illness in the United States. We are inviting people to participate by a variety of means. But one of them is through the community health centers here included in the health provider organizations, because we have a very specific goal here of having at least 50 percent of the participants in All of Us being individuals that are underrepresented traditionally in medical research programs.

The community health centers, who provide care to a great number of people, particularly those in lower socioeconomic situations, are very excited about being our partners, and we're excited about having them as partners. We're starting with the six, and glad about Middletown as a place that has clearly been very successful in getting this up and going. But that is a pilot to see if we can, in fact, enroll many more. We aim to launch this project fully next spring. At the moment, we're in a beta test. We've enrolled about 12,000 individuals. We're learning everything we can about how these moving parts can all work together, and it's looking very good.

Senator MURPHY. Great. Thank you, Dr. Collins.

Dr. Gottlieb, I want to switch topics to another exciting development out of the Cures Act. This is the establishment at the FDA of the Oncology Center for Excellence, which creates a cross-center team to work together on a variety of products to treat cancer. Just an update on what you've learned thus far from this model, and what do you take into account when you're thinking about creating other disease specific offices?

Dr. GOTTLIEB. Having gone to college in Middletown, Connecticut, I appreciate the shout-out from the Senator.

Senator MURPHY. Thanks.

Dr. GOTTLIEB. This is an extremely important effort on the part of the agency, so I appreciate your asking the question. The Oncology Center for Excellence—what we've essentially tried to do is consolidate the clinical portion of the review of oncology products into one combined center. So this was instrumental in our ability to expedite the review of the CAR-T products, for example. By consolidating the clinical expertise, we're able to more efficiently look at some of the biologics.

We've had challenges fully standing it up, and in all candor, it's related to fully funding it. We believe that this is the future of the agency, though, trying to get these consolidated programs in place, and we're looking to other therapeutic areas where we can do this. But I think before we can progress on to other therapeutic areas,

we really need to make it work in the oncology setting. So we're looking forward to continuing to try to move this program forward.

Senator MURPHY. Great. Another reminder to us that we've got to give you the funds to implement this act.

Quickly, back to you, Dr. Collins. One more question, and that is on another part of the 21st Century Cures Act. Senator Isakson and I worked on a provision that allows for the CDC to collect information on the incidence and prevalence of neurological diseases. This was the Advancing Research for Neurological Diseases Act that Senator Alexander and Senator Murray helped us include in this legislation. Just talk for a second about the importance of having this data on neurological diseases to research done at NIH.

Dr. COLLINS. Well, it's incredibly helpful to know what incidence and prevalence is for neurological conditions, particularly a condition like Parkinson's, but there are many other disorders as well. It is challenging and expensive to do that kind of analysis and to do it effectively and to keep it updated. As I understand it, while CDC was given the charge to do this, at the present time, they do not appear to have the funding to carry it out.

Senator MURPHY. Great. All right. You've got another advertisement to put the money behind the legislation we passed.

Thank you very much, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murphy.

Senator Hatch, a former Chairman of this Committee, welcome.

Senator HATCH. Well, thank you so much, Mr. Chairman. I appreciate it.

I certainly appreciate you two gentlemen. I think you're both some of the best public servants I've seen in all of my 40-plus years in the U.S. Senate, and I'm proud of both of you, and I hope you'll just keep doing what you're doing. So I want to thank you both here today.

Dr. Gottlieb, last Congress, I joined Senator Bennet in authoring the PATH Act which was included in the 21st Century Cures Act and will help advance the development of urgently needed new antibiotics for multidrug-resistant infections by allowing them to be studied in smaller, more rapid clinical trials and, therefore, approved more quickly for the patients who need them most. As you know, FDA was tasked with developing guidance for industry regarding this limited population pathway, or LPAD. Can you please detail the ways in which stakeholder input is being solicited and incorporated into the guidance?

Dr. GOTTLIEB. Thank you for the question, Senator. We plan to issue the guidance that you reference in the spring, and we've been meeting with stakeholders and other interested parties in the development of that guidance, consistent with our good guidance practices. So we will have stakeholder meetings in the development of any guidance document.

I'll just say we think that this is an extremely important pathway, and we've already had multiple IND meetings with sponsors and believe this will be a robust vehicle for trying to create new pathways for drugs targeting significant unmet medical needs.

Senator HATCH. Well, thank you.

Dr. Collins, I was pleased to see that as a result of 21st Century Cures the NIH was able to start the Regenerative Medicine Inno-

vation Project and that several of the first awards from this initiative had gone to research on rare diseases. As you may know, I've been a champion of the rare disease community for quite some time, and I applaud you for also recognizing how vital research in this area truly is.

Strides in regenerative medicine may prove to be truly transformational in the way we understand and possibly even treat rare diseases.

What barriers do you foresee in expanding research into this area as the Regenerative Medicine Innovation Project continues?

Dr. COLLINS. Well, thank you, Senator, for the kind remarks at the beginning of your time and also for the question. I think this is an enormously exciting time for rare diseases because we have tools now that are starting to work. Dr. Gottlieb referred a little bit ago to gene therapy. I couldn't help but point out today in the *New England Journal of Medicine* a really dramatic advance in hemophilia using gene therapy with a viral vector to deliver the gene to the liver of men who are affected—and it's men because it's an X-linked condition—with really remarkable benefit over the course of many weeks. That's just a single example of what's possible in this space.

I mentioned a little earlier my hopes that we could cure sickle cell disease by taking out the bone marrow cells, correcting the sickle mutation, putting them back. It's a transplant to yourself. It's a gene editing approach, which we also find to be very exciting.

Recently, this terrible disease called spinal muscular atrophy, SMA, which results in children who are born, seem to be okay, and then develop paralysis and often don't live past their first year—now, with a clinical trial recently published, some of these kids are making it to their prekindergarten and looking pretty good, again by a genetic change that's been introduced using either a virus or a gene editing strategy.

I think the big barriers right now is to just push the science as hard as we can, and the Cures Bill helps us by giving us that kind of inspiration. I'm glad to say the barriers with regulation are not the issue right now, working with Scott and his colleagues at FDA who also have made rare disease a very high priority. Of course, there is this issue about investment. Companies may not be so interested in putting a lot of money into a very rare disease because the market's going to be small, which means NIH has an even stronger responsibility to de-risk those projects and push them as far down the road as possible.

One more thing I would say that you did for us in the Cures Bill is to make it possible for us to run Phase III trials for rare diseases in the Therapeutics and Neglected Disease Program in NCATS, which we had not previously had the privilege of doing and which we will be using aggressively for this purpose.

Senator HATCH. Well, thank you. Dr. Collins, one of the provisions of the 21st Century Cures was designed to improve opportunities for young and emerging researchers. I've heard from the University of Utah, which receives, I think, around \$150 million in NIH grants annually, that they have seen an improvement in this area, and for that, I would like to thank you and your staff and your work in this area.

My time is up so I'll just thank you and tell you how much I appreciate your willingness to serve in this government and how much you really mean to people like us who have worked all these years in these areas.

Dr. COLLINS. Thank you, Senator.

Senator HATCH. Thank you.

The CHAIRMAN. Thank you, Senator Hatch.

Senator Baldwin.

Senator BALDWIN. Thank you, and I want to add my words to the others of congratulations for the bipartisan work you led, Mr. Chairman and Ranking Member Murray, on the 21st Century Cures Act.

Thank both of you, Dr. Collins and Dr. Gottlieb, for your service.

During the Committee deliberations on 21st Century Cures, I regaled the Committee any number of times about being the granddaughter of an NIH-funded scientist and how that influenced my championing of strengthening our research enterprise and support for the NIH. But in my first year in the U.S. Senate, in 2013, I had a particularly powerful and inspirational meeting with a young man, a high school senior. His name is Ian, and he is a bone cancer survivor from Fond du Lac, Wisconsin.

Ian told me that cancer research, no doubt, helped save his life, and that's why he wanted to grow up to be a scientist, to help others with his disease. But he was concerned that it wouldn't be possible for him to break in as a new researcher due to his awareness of NIH funding cuts at the time.

Ian inspired me to author the Next-Generation Researchers Act, along with my colleague, Senator Collins, to fight to improve NIH opportunities for new and early stage researchers. I am proud to report that Ian recently graduated from college, where he was helping a researcher at the University of Minnesota study the genetics of osteosarcoma, and he is now working with a scientist at Huntsman Cancer Institute in Salt Lake City, Utah, on pediatric cancers.

Dr. Collins, I'm encouraged that the NIH has begun to robustly implement the Next-Generation Researchers Initiative to help support future scientific leaders like Ian as they discover cures for cancer and pursue other lifesaving research. You announced a new policy this year to issue more awards to investigators in the earliest parts of their independent research careers to help them sustain or achieve research independence.

I'd like it, Dr. Collins, if you could please describe how each institute and center will prioritize awards for these early and mid-career investigators and how this will help improve and stabilize opportunities for our next generation of researchers.

Dr. COLLINS. Well, thank you for the question. You're touching on a personal passion that I feel and that many of the other institute directors do as well. We actually just published about a month ago, myself and Michael Lauer and Larry Tabak, a description of what this policy is and how we're going to implement it, because we passionately agree with you that the next generation is really critical for our future, and it has been a tough period with the loss in purchasing power that NIH sustained between 2003 and 2015. Those first-time, early stage investigators were having a hard time getting started, and we cannot lose that, and we were starting to.

Each one of the institutes, depending on where they think they can find their flexibilities, are freeing up dollars to make it possible for those early stage investigators who otherwise would just miss the pay line to actually get funded. We started this quite late in fiscal year 2017, but we were able to make a whole bunch of awards that otherwise would not have happened, and we're not done yet, because we're actually trying to see if we can reach back into some of those fiscal year 2017 reviews and fund a few more of those.

We will have a meeting next week of my advisory committee, where we have a working group which you would be interested in, because it has graduate students and post-docs and junior faculty, not just the gray eminences, but the people who are really involved in this, and we will have a deep discussion about whether we have the right plan here in order to make this particular priority really happen.

Senator BALDWIN. I can see I'm running of time, but I want to just note—maybe you can answer for the record—that you estimate that this new effort to prioritize more awards for early investigators would be about \$210 million in the next year and \$1.1 billion over the next 5 years. Does NIH need additional resources for this policy to ensure that it fulfills its promise and continues to advance all other critical NIH efforts?

Dr. COLLINS. Very quickly, we are prioritizing this within our existing resources, but, of course, we can do more of it if the resources are available.

The CHAIRMAN. Before we go to Senator Warren, let me recognize Senator Murray.

Senator MURRAY. Thank you very much, and I just want to thank both of you for your answers, and I will be submitting more questions for the record. I have another commitment I have to make.

[The following information can be found on page 51 and 61 in the appendix:]

Senator MURRAY. This has been an excellent hearing, Mr. Chairman. I really appreciate it, and we have another one next week on the mental health part of Cures. I think it's really educational for all of us and appreciate both your efforts, and I look forward to continuing to work with you.

The CHAIRMAN. Thank you, Senator Murray.  
Senator Warren.

Senator WARREN. Thank you, Mr. Chairman.

We've been talking about the Cures Act. It has a lot of bipartisan provisions that I'm really glad became law. During our recent hearing on gene editing, we discussed new genetic privacy protections for research participants that Senator Enzi and I have worked on together. Right now, Massachusetts biotech companies are benefiting from a provision that Senator Bennet and Senator Burr and Senator Hatch and I wrote to try to clarify the FDA's authority relating to gene therapies for rare diseases, and I could go on. It's a long list.

But Cures also fell short in a really big way, and that's on funding. I led Democrats on this Committee in calling for an extra \$50 billion for the NIH and the FDA, and Cures did not send one single

new dollar to these agencies. Instead, it only said that future Congresses might spend about 10 percent of that amount on NIH and FDA, and I'm glad that so far Congress has been increasing NIH funding. But I don't think it's time for us to pat ourselves on the back yet over where we are in funding the NIH.

Dr. Collins, let me just go through this a little bit. Does the NIH fund most of the grant applications that it receives from scientists?

Dr. COLLINS. No, we certainly aren't able to do that. We fund about 19 percent of those because that's the way it comes out after we do the priority scoring and see how much money we have.

Senator WARREN. Okay. So out of every 100 applications you get, you're funding about 19 of them. Now, is that because the other 81 would have been bad investments that would not have helped us make biomedical breakthroughs to advance science?

Dr. COLLINS. If we look back in history, say, back around 2000, 2001, we were funding about 30 percent, maybe even 35 percent, because the funds were more available. We've looked at those to see—did a grant that scored at the 25th percentile actually turn out to be less productive than one at the 15th percentile? The answer is no. We can't really tell the difference up to about the 30th percentile. Even though peer review is trying to draw distinctions, it's very hard to do so in that top third.

Senator WARREN. In other words, if we—roughly, just using the numbers you had here—if we doubled, for example, the number of grants that we were able to fund, you think there's still a lot of good science to be had out there.

Dr. COLLINS. I think there would be fantastic science out there.

Senator WARREN. Okay. That's powerfully important. I want to follow-up, too, on the point that Senator Baldwin made and the discussion you all had about researchers in the early part of their career. Getting that first NIH grant can make or break an academic career. It can be the difference between whether the scientist stays in the field or whether the scientist has to leave academic medicine and go somewhere else.

I just want to ask more about the details here. Where are we right now on early career researchers? What percentage of the grants are they able to get?

Dr. COLLINS. Well, beginning in 2008, we actually instituted a policy so that those applicants who came to us for the first time as a principal investigator got a bit of a boost. They competed against each other, essentially, as opposed to against the most experienced ones, which meant, effectively, in priority score terms, they got a few extra points. But that's not good enough. We are still losing lots of those, and their success rates for those early stage investigators—we're still well below what we'd want to see.

Ultimately, we think it would be most healthy if at least, say, 25 percent of those applications were going to get funded, and that's what we're trying to do with this new initiative, the Next Generation Research Initiative, which is named specifically for the words that were used in the bill. Thank you, Senator Baldwin, for that encouragement.

Senator WARREN. But I understand right now, we've been at about 16 percent. Is that right? You're saying at a minimum, we ought to be boosting that to about 25 percent.

Dr. COLLINS. We've looked closely at every institute's successes and tried to figure out how we can get there with this new policy, yes.

Senator WARREN. I know that NIH has done what it can in this area. But NIH funding is still down about 15 percent of where it was a decade ago, back when we had a 50 percent higher success rate for the proposals that were coming across reviewers' desks. The Cures Act did not solve this problem. Frankly, it didn't even come close, and that's why today we're reintroducing the National Biomedical Research Act, which provides \$50 billion in new funding for the NIH and for the FDA. I see you're sitting up straighter there, Dr. Gottlieb.

[Laughter.]

Senator WARREN. This legislation is co-sponsored by Senators Sanders, Casey, Franken, Bennet, Whitehouse, Baldwin, Murphy, Kaine, and Hassan, all the Members of this Committee, as well as several of our Democratic colleagues who are not on the Committee. Families across this country are waiting for medical breakthroughs, and researchers are waiting for the money to fund their work so they can make those breakthroughs. It's time for us to step up and put more money into NIH. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Warren.

Senator HASSAN.

Senator HASSAN. Thank you, Mr. Chair, and I'll add my thanks to you and the Ranking Member for this hearing and for your work on the Cures Act.

To Doctors Collins and Gottlieb, thank you so much for being here, and would you please—along with us thanking the two of you for your service and leadership, please thank the women and men who work with you every day in your agencies for the extraordinary work they do on behalf of the people of the United States.

Dr. Gottlieb, I wanted to start with a question or two for you. We have discussed the devastating impact that the opioid epidemic is having in New Hampshire and all across the country. One of the tools in combating the epidemic is medication-assisted treatment, like buprenorphine. It plays an important role in recovery along with access to other services and supports.

Both of you, I think, mentioned in your opening comments the possibility that we will develop non-addictive pain products, which would help prevent addiction when, for example, somebody gets in an accident and is prescribed an opioid and then becomes addicted. The 21st Century Cures Act took some important steps on patient-focused drug development, including requiring guidance on patient experience data.

Dr. Gottlieb, can you discuss how patient-focused drug development initiatives could be used in relation to developing new medication-assisted treatment and the development of new non-addictive pain treatments?

Dr. GOTTLIEB. I appreciate the question. The bottom line is they can be a very important tool, and I think the provisions that are in the Cures Act are going to help inform how we go about thinking of the parameters that we use to encourage the development of products, both kinds of products, both non-addictive alternatives to



some of the opioid products, but, in particular, medication that can assist people to live lives of sobriety.

We have committed to publish—to develop new guidance documents for outlining the pathway for the development of medically assisted therapy. We want to create incentives for sponsors to come in and try to develop those products, and part of that is making sure we have very clear guidelines.

As part of that, we're going to be looking at alternative endpoints that we haven't looked at in the past, for example, issues like craving. We know craving is a factor that leads people to continue to use opioids, and if that can be an endpoint in the trials that we use to assess new products, it might provide a more efficient pathway, and that certainly is informed by the work we do with patients and looking at patient-informed endpoints.

Senator HASSAN. Thank you.

Dr. Collins, I wanted to talk to you, too, about—you made a comment in a response, I think, to Senator Alexander about the impact of the Other Transaction Authority that you now have. Can you comment a little bit about how that could be helpful in the opioid space? You said it would be, but how specifically would OTA be useful to the NIH and its work in doing opioid disorder research?

Dr. COLLINS. The plan that we have put in place, which is going to be fleshed out in more detail next week in an intense 2-day meeting, will involve a lot of rapid action, both to come up with new ways to treat addiction, because we need more options to treat overdoses that don't respond as well as they might to fentanyl, and to develop these new non-addictive pain medicines that everybody agrees—that's going to require partnerships between academic institutions that have the appropriate science skills, with industry that may have formulation capabilities or drug development pathways.

If we have to build that on the process of issuing grants and contracts in the traditional way, it's going to take a long time. Other Transaction Authority allows us to do something in maybe 6 weeks that might have otherwise taken 9 months. We've learned how to use this effectively and responsibly for the All of Us Program for the common fund, and we think this would be a great place for it to be available. We will be careful about how to use it, but it could help us a lot.

Senator HASSAN. Well, thank you. Finally, I wanted to talk a little bit about our new generation of scientific researchers, because both Senators Baldwin and Warren were talking about that. Cures took important steps for the next generation of researchers by helping to make it more affordable for prospective students to pursue their graduate degrees in science and engineering. NIH has been responsive to these efforts and in September announced a new policy for implementing special funding consideration for these graduate students.

In recent weeks, I've heard from a number of graduate students, Dr. Collins, who are fearful of how the Republican tax legislation, particularly the House version of it, could impact their ability to pay back their student debts and whether it could even force them to drop out of their programs. One particular provision in the House bill would require that graduate-waived tuition is taxed with

their stipends, a change that I've heard from Ph.D. candidates could really impact—one wrote, “This would triple my taxable income and increase my yearly taxes by more than \$10,000. It would force me to drop out of school because I wouldn't be able to afford rent and groceries while earning below the poverty line.”

Can you comment, Dr. Collins, on what you think this provision would mean for the future of our young researchers and biomedical research?

Dr. COLLINS. Well, very quickly, because of the time, these are our future graduate students that are learning to be the next generation of leaders in science across many disciplines. But, certainly, I think of life sciences needing those individuals to be the ones who are going to make the next breakthroughs. Anything that happens to discourage the best and brightest from taking that track or to feel that they can't afford to do so is something we should approach with great concern.

Senator HASSAN. Thank you very much.

The CHAIRMAN. Thank you, Senator Hassan.

Senator Whitehouse.

Senator WHITEHOUSE. Thank you very much, Chairman, and I join my colleagues in congratulating you and Ranking Member Murray on the success of a year ago. I hope we have more to come.

Dr. Collins, one of the things we got into the Cures Act was a request that you reduce the burden of what we call low-risk sub-recipient monitoring. I just left Brown University's Director of Research, who was in the anteroom a moment ago, and this was also the University of Rhode Island's request—you get things like Brown University and University of Rhode Island working together on a project, and the supposed obligation to monitor the sub-contractors now applies to each of them.

You have URI monitoring Brown, Brown monitoring URI. They're both monitored by you and OMB. Can you help reduce the bureaucratic and reporting burden related to sub-recipients?

Dr. COLLINS. Senator, we don't particularly enjoy doing that kind of low-risk monitoring, either, and we have, in fact—thank you to the Cures Bill—put together a proposal of a way that we might reduce the amount of low-risk sub-recipient monitoring. There are certain situations that maybe don't quite meet that, but many of them do, and those are—

Senator WHITEHOUSE. Please include us in that cycle so that we can be helpful in giving advice and making sure that goes forward at a good pace.

Dr. COLLINS. Be happy to.

Senator WHITEHOUSE. Dr. Gottlieb, the Cures Act was very good at getting FDA to connect the device and the drug sides a little bit better, and you've done a lot of training to try to connect the two. But the original testimony that we had from FDA from both the drug and the device sides was that what you really needed was a third pathway for drug-device combinations.

Would you assure us that if it turns out that the hybrid effort that the Cures Act established isn't doing the job that you will let us know so we can take a second crack at it legislatively?

Dr. GOTTLIEB. Absolutely, Senator. This has been a challenging area for us over a period of time. We think that the provisions in

the Cures Act give us a lot of new tools to address it. We're going to be implementing those provisions and have some guidance pretty soon that we think will articulate a better pathway. But if it doesn't resolve the challenges that you've identified in the past, I'd absolutely be delighted to talk to you about alternatives.

Senator WHITEHOUSE. Great. Thank you. Just so long as we're staying in touch and in the loop and not wasting time if it turns out not to be productive.

Dr. Collins, there have been some very everyday moments that are actually very significant. Back in 1876, a gentleman called his assistant, Watson, to come into the room, and in 2012, a lady named Cathy Hutchinson took a sip of coffee—pretty minor things except for the technology involved.

“Come here, Watson, I need you” was Alexander Graham Bell first using the telephone to summon his assistant, and Ms. Hutchinson picked up the cup of coffee and brought it to her lips through what at Brown University they call the BrainGate, which is electrodes in the brain so that by mere thought, she could control the robotic arm. The brain technology that NIH is funding is terrific. Are you satisfied that you're adequately connected with DARPA, which is the BrainGate funding, to make sure that everybody is pulling in the same direction?

Dr. COLLINS. We are enormously excited about that as well, and, yes, we have worked quite closely with DARPA in this whole idea about how you could begin, for people who are paralyzed, to control a robotic arm to carry out fairly sophisticated activities, including the ones you mentioned. This is a big part of what the BRAIN Initiative—which involves NIH and DARPA and NSF as well as the Department of Energy as well as some international partners—aims to do, is to really figure out how those 86 billion neurons between your ears do what they do in these complicated circuits which we're beginning to take apart and understand even better.

We would like to go from where we are now, which was sort of an empirical effort to get this to work, to really understand it so well that you knew exactly where to place those electrodes to get the maximum sophistication of the move of that robotic arm.

Senator WHITEHOUSE. Last topic. We've just done some good bipartisan legislation on plastics in the ocean here in the Senate. The U.N. has just issued, I think, a unanimous statement of concern about plastics. Plastic, as you know, doesn't biodegrade. It just breaks down into smaller and smaller and smaller points, and then microscopic creatures can consume it, and it begins its track up the food chain.

Never in human history have we had to experience that kind of plastic loading into our diet. It's now found in tap water. It's found all over the place. It's obviously going to be in our food. Is this something that the National Institutes of Health should begin doing some basic research on so that if this turns out to be a problem—it's certainly a new experience for humankind to have to digest and process that kind of microscopic plastic in the food chain—that you're alert to it?

Dr. COLLINS. Absolutely. The National Institute of Environmental Health Sciences, one of our 27 institutes, but the one that's located in North Carolina in Research Triangle Park, is already

looking at this. I can give you a summary of where we currently stand in terms of the research that's being conducted.

Senator WHITEHOUSE. I'd appreciate that. We can do that offline and through your staff.

Dr. COLLINS. Be happy to.

Senator WHITEHOUSE. Thank you, Chairman.

The CHAIRMAN. Thank you, Senator Whitehouse.

Thanks to both of you for being here today. I hope you'll follow-up with the memo on regenerative medicine sometime in the next few weeks that I can give to Senator McConnell and other Senators who are interested in that. You heard several Senators mention that today, and you have quite a story to tell, I think.

Also, we'll be interested as we look toward a second anniversary of the Cures Act in a year to—especially at how we're taking that 10 or 12 years between idea and something in the medicine cabinet, something in the doctor's office—how we're compressing that, how we're setting priorities, and how FDA, NIH, and CMS are working together to do that. I salute you for the steps you've already taken, but that would be a very promising way to do things, and, really, you have to do that more than we. We could do some things in legislation, but that we really can't do as well.

We could order you to do it, but that wouldn't make you do it. You have to do what you've already started to do, which is to work together to speed that up and still do it in a way that provides safety and efficacy.

Without getting you in the middle, Dr. Collins, I sometimes worry that the messages that come out of Washington aren't—are heard by the graduate students and the researchers across the country, and they worry that we're not funding their work. If the President's budget, for example, says one thing, and everybody pays a lot of attention to it, and then that really doesn't happen, nobody knows it doesn't happen.

I remember that in President Obama's last year, he actually reduced recommended funding—discretionary funding for the National Institutes of Health, and he recommended a big increase in mandatory funding for the National Institutes of Health.

Now, this isn't too hard for people to understand. This is the authorizing Committee. We don't appropriate money, usually, or we can't appropriate money, and we have another committee, which Senator Murray actually is the Ranking Member of and Senator Blunt is the chairman of, and that's the money committee. So for us to appropriate, say, \$50 billion dollars in new funding for the National Institutes of Health is a wonderful aspiration, but that's not what we do.

We decide, for example, whether Dr. Gottlieb should have a new breakthrough path for medical devices. If the Appropriations Committee were to decide that Dr. Gottlieb should have a breakthrough path for medical devices, we would be very upset, because we'd say, "That's our job." If we were to try to appropriate another \$50 billion for you, the Appropriations Committee would be very upset because they'd say, "That's our job."

Let me ask you this. We have discretionary funding. That's the Appropriations Committee. We have mandatory funding, which

this Committee could do. What's the size of the NIH budget this year? What's your total funding?

Dr. COLLINS. \$34 billion.

The CHAIRMAN. How much of that is biomedical research?

Dr. COLLINS. Virtually all of it, and, to be clear, more than 80 percent of that goes out to all those institutions all over the country that do that research.

The CHAIRMAN. How much of that \$34 billion is mandatory funding?

Dr. COLLINS. I think there's \$150,000 in there.

The CHAIRMAN. Almost all of it is money that's supplied by the Appropriations Committee—

Dr. COLLINS. I'm sorry, \$150 million for Type I diabetes.

The CHAIRMAN —through the subcommittee that Senator Blunt and Senator Murray do. Now, 2 years ago, if I'm correct, Senator Blunt and Senator Murray recommended and the Congress approved a \$2 billion increase in funding for the NIH.

Dr. COLLINS. Yes.

The CHAIRMAN. Last year, they recommended and Congress agreed and the President signed another \$2 billion increase for NIH.

Dr. COLLINS. That's right.

The CHAIRMAN. If I'm not correct, I believe the Committee has recommended another \$2 billion for the third year in a row. The Congress hasn't yet acted. The way we normally do things here is once we put something in the budget, we count it for 10 years. So the first year is \$2 billion. That's \$20 billion over 10 years. The second year is \$2 billion. That's another \$20 billion over 10 years. The third one, if we do it this year, another \$20 billion over 10 years.

Now, that's not guaranteed, but that's usually what we do. We put it in the base, and we expect to do it again. With the priorities that we have in this Committee and in the Appropriations Committee, I expect that to be the case.

Then, in addition, we did something that was very unusual in the Cures Bill, very hard to do. We took \$4.8 billion, created a hybrid sort of funding that created all kinds of consternation with the House of Representatives and with our Appropriations Committees, and we gave some special funding to the Precision Medicine and the Cancer Moonshot, the BRAIN Initiative, and some other things. But the chances of that happening again are close to zero.

The real money that is supposed to go to the National Institutes of Health and NIH comes through the Appropriations Committee, and they've been doing a tremendous job over the last few years, and I say that—I'm a member of it myself, but I'll give Senator Blunt and Senator Murray great credit for squeezing out of the budget resources which are a good deal larger than in the last few years.

There's nothing wrong with aspiring for more. There's nothing wrong with looking back 15 years and saying that if we had gone up at the same rate we had been going up, it would be even higher today. But I think it's important for researchers across the country to know that this Congress in a bipartisan way for the last 3 years has been extraordinarily committed to significant increases in

funding for the National Institutes of Health, and I think it's made a difference.

Dr. COLLINS. Senator, I really appreciate your taking the time to explain all that, because I think there are people watching who are wondering how these decisions get made and where we are. Certainly, there have been a lot of anxieties in the biomedical research community, particularly from young investigators, about what is going on and what's the likelihood of a pathway.

You have pointed out that there's a great deal of reason to be excited and optimistic about a career in biomedical research, first of all, because the science now is so incredibly promising and exciting, but, second of all, because the support, as you've outlined, has been on the upward trajectory, with 2 years already with this \$2 billion increase already happening and a significant promise that it may happen for the third. If that were to be the case, that would be about a 20 percent increase for NIH over the course of 3 years, which is a very encouraging sign.

Again, I'm grateful that in this era where so few things seem to be bipartisan, medical research continues to be so, and much credit to you and your colleagues for keeping that alive.

The CHAIRMAN. I'll ask one last question of Dr. Gottlieb and you. With all this excitement and these breathtaking biomedical advances, do you see any—as you talk to high school students or college students, do you see any increase in an interest in biology?

Dr. GOTTLIEB. I don't talk to high school and college students that much. I will tell you that—my girls are eight and four. I think that there is an increase in excitement among those training in medicine right now about what the future holds. I will affirm that. I have a lot of contact with residents and medical students, and I see an increased excitement about what they're going to be able to accomplish over the course of their careers that I couldn't accomplish over the course of my medical career.

The CHAIRMAN. Dr. Collins.

Dr. COLLINS. Well, certainly, when I go out to universities to give a talk and meet with students—and I always do that. That's the best part of any visit to an academic center, is to say, "I want a chance to meet with the graduate students and the post-docs, and I don't want anybody else in the room, because I really want to hear from them."

I have heard a lot of anxiety in the last couple of years, and I'm trying to reassure people that things are looking much brighter than they think they are. That sort of sense out there of trouble is probably beyond what it maybe ought to be considering the path that we're on. But, boy, do I hear excitement about the scientific opportunities.

If you can quickly switch to that topic, then the spark goes into the conversation, and the eyes light up, and this graduate student tells you about the experiments they're doing that week and how excited they are about what they can do, because there are things that a single student can do right now that might have taken a team of 10 people or 5 years to do.

The technology has come along so quickly and the ability to use big data and computational approaches. This is the golden era, and

if anybody really wants to have a great time in science, they should come and join us.

I hope Ian, whoever that is, that Senator Baldwin was talking about will be one of those as soon as possible, because we need this. This is our future. We want the best and brightest to join us so that this can happen.

The CHAIRMAN. Well, thanks to both of you.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time if they would like.

Our Committee will meet again next week on Tuesday, December 12th, at 10 a.m. for a hearing titled, The Cost of Prescription Drugs: An Examination of the National Academies of Sciences, Engineering, and Medicine Report, Making Medicines Affordable, a National Imperative. This is the third in our hearings on drug prices, which has been requested by both Democratic and Republican Members of our Committee.

Then next Wednesday, we have our oversight hearing on the mental health aspects of the Cures Act.

Thank you for being here today. The Committee will stand adjourned.

[Additional Material follows:]

## QUESTIONS AND ANSWERS

RESPONSES BY FRANCIS COLLINS TO QUESTIONS FROM SENATOR MURRAY, SENATOR CASSIDY, SENATOR COLLINS, SENATOR ROBERTS, SENATOR WARREN, AND SENATOR WHITEHOUSE

### SENATOR MURRAY

*Question 1.* In the 21st Century Cures Act, I was also proud to champion provisions to improve the inclusion of historically underrepresented populations—including women, racial and ethnic minorities, children, and seniors—in clinical research. These provisions include requiring NIH to report on the inclusion of these populations in NIH-supported research.

In each institute or center's strategic plan, Section 2031 requires the directors of the national institutes and national centers within NIH to include details on how it accounts for women and minority populations in clinical research to reduce health disparities after consulting with the National Institute on Minority Health and Health Disparities and the Office of Research on Women's Health.

In the NIH Triennial Report (formerly biennial), Sections 2032 and 2038 require the NIH to include or identify:

- Study populations by demographic variables, including biological and social variables and relevant age categories, such as pediatric subgroups.
- The number of women as well as the number of minority groups included as subjects, and the proportion of subjects that are women or members of minority groups, in any project of clinical research conducted during the applicable reporting period, disaggregated by categories of research area, condition, or disease, and accounting for single-sex, single-race, and single-ethnicity studies.
- For the applicable reporting period, the number of projects of clinical research that include women and members of minority groups and that have been completed during such reporting period and are being carried out during such reporting period and have not been completed.

In the agency's assessment of research priorities, Section 2038 requires NIH to publicly post and assemble data on study populations of clinical research at each national research institute and centers, specifying the inclusion of women, members of minority groups, relevant age categories (including pediatric subgroups), and disaggregating the data by research area, condition and disease category.

a. Could you provide an update on NIH's progress in implementing these provisions and the agency's plans to make this reporting required for all studies?

Answer 1. NIH is committed to supporting clinical research that benefits individuals of all sexes/genders, races, ethnicities, and ages. Appropriate inclusion of research participants is essential to ensuring that NIH is supporting sound science that will ultimately inform clinical practice to the benefit of all who are affected by the disease or condition under study.

NIH has longstanding policies to ensure appropriate inclusion of women, minorities, and children in its supported clinical research studies. For more than two decades, NIH has collected data on the distribution of study participants by sex/gender, race, and ethnicity, with aggregate data available online.<sup>1</sup> In addition to continuing these procedures, NIH has taken the following steps to implement inclusion reporting-related provisions of the 21st Century Cures Act:

- In August 2017, the Directors of NIH Institutes and Centers (ICs) were informed that all IC strategic plans must account for women and minorities as well as be focused on reducing health disparities.
- On December 19, 2017, NIH announced a revised Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects.<sup>2</sup> The policy, developed after significant input from experts and the public through a Request for Information<sup>3</sup> and workshop<sup>4</sup>, requires all applications submitted for due dates January 25, 2019 or later that propose research involving human subjects to address inclusion of individuals across the lifespan (including children and older adults) and provide de-identified individual-level data describing participant age, sex/gender, and race/ethnicity in progress reports.
- NIH is enhancing its electronic systems to accept de-identified individual-level data on sex/gender, race, and ethnicity (functionality expected this summer). Leveraging data that many investigators are already collecting in a format consistent with the way these data are typically obtained and stored is expected to maximize analytic flexibility while minimizing administrative burden.
- The Human Subjects and Clinical Trials section of the NIH application forms has been updated to consolidate human subjects, inclusion enrollment, and clinical trial-related information in one place, and expand the information required for proposed clinical research studies.<sup>5</sup> Among the changes are structured data fields that capture the expected age range of participants. Beginning January 25, 2018, investigators submitting competing applications that include research involving human subjects are required to specify the minimum and maximum age of participants in the proposed study.
- The NIH Office of Extramural Research is developing methods to extract data on the inclusion of women and minorities by research area, condition, and disease category for each IC. These data will account for single-sex, single-race, single-ethnicity, completed, and non-completed studies. Further, these data are expected to be published in the next NIH Triennial Report published online.

NIH looks forward to the availability of additional data on the diversity of participants in clinical research studies. These steps will help us better understand the distribution of participants in our clinical research, and how interventions work in their intended populations. These better data will allow us to make more informed decisions going forward and improve the health of all citizens.

*Question 2.* I was pleased to see that NIH formed a Child Enrollment Scientific Vision Working Group (CESVWG) to support the inclusion of children in the All of Us Research Program as part of the Precision Medicine Initiative, which the 21st Century Cures Act authorized in Section 2011.

a. Can you provide an update on the status and expected release date of the report from the CESVWG, as well as information on NIH's plans for subsequent efforts to oversee the inclusion of children in the All of Us Research program after CESVWG sunsets?

b. Do you intend to have a specific funding opportunity focused on pediatric enrollment to support an adequate sample size, particularly for conditions such as pediatric rare diseases?

<sup>1</sup> <https://report.nih.gov/recovery/inclusion—research.aspx>

<sup>2</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>

<sup>3</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-059.html>

<sup>4</sup> [https://report.nih.gov/UploadDocs/NIH\\_percent20Inclusion\\_percent20Across\\_percent20the\\_percent20Lifespan\\_percent20Workshop\\_percent20Summary\\_percent20Report\\_percent20—FINAL—508.pdf](https://report.nih.gov/UploadDocs/NIH_percent20Inclusion_percent20Across_percent20the_percent20Lifespan_percent20Workshop_percent20Summary_percent20Report_percent20—FINAL—508.pdf)

<sup>5</sup> <https://grants.nih.gov/policy/clinical-trials/new-human-subject-clinical-trial-info-form.htm>



Answer 2, a., b. The Child Enrollment Scientific Vision Working Group (CESVWG), an expert working group of the All of Us Research Program Advisory Panel, first convened in the summer of 2017 and completed its work in late 2017. The final report of the working group, posted publicly on January 18, 2018, describes the types of research that All of Us is uniquely positioned to enable through the enrollment of children. All of Us is now considering the information gathered by this working group with a focus on maximizing the utility of the research program on a wide range of pediatric research opportunities in the near-, medium-, and long-term. There are several program modifications that will need to be made prior to enrolling children, including changes to the initial research protocol. The consortium, comprised of All of Us NIH staff, awardees, and partners, is actively working on all components of the program (engagement, consent, assessments, return of information, etc.) to identify pediatric alternatives to the current adult versions. As All of Us considers the steps it needs to take to include children, the Program will make decisions about any funding opportunities.

*Question 3.* Section 2034 of the 21st Century Cures Act calls on NIH and other entities across the executive branch to review policies and regulations with the objective of reducing administrative burden for researchers.

In October, the Federation of American Societies for Experimental Biology (FASEB), the Association of American Medical Colleges, the Council on Governmental Relations, and the National Association for Biomedical Research issued a report with recommendations for reducing regulatory burden while maintaining animal welfare.

a. Do you plan to incorporate any of the recommendations from this report in your review and analysis of regulations and policies regarding the care and use of laboratory animals, as required by Section 2034?

b. What is NIH's plan to seek stakeholder input on reducing regulatory burden for the research community, especially regulations related to use of animals in research?

Answer 3, a., b. NIH has undertaken many efforts in recent years to clarify and reduce administrative burden associated with animal care and use to the extent possible under current mandates. Section 2034(d) of the 21st Century Cures Act specifically requires that the NIH in collaboration with the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) complete a review of applicable regulations and policies for the care and use of laboratory animals and reduce administrative burden on investigators. The NIH Office of Laboratory Animal Welfare, USDA Animal and Plant Health Inspection Service—Animal Care, and FDA established a working group in February 2017 to address the requirements of the Act.

The working group will review applicable regulations and policies for the care and use of laboratory animals as well as reports and surveys recommending approaches to reduce regulatory burden on investigators, while maintaining the integrity and credibility of research findings and protection of research animals. This includes considering the October 2017 recommendations from the Federation of American Societies for Experimental Biology, the Association of American Medical Colleges, the Council on Governmental Relations, and the National Association for Biomedical Research.

Further, the group will use several approaches to consult with stakeholders on reducing regulatory burden for the research community. For example, NIH will solicit input with a Request for Information (RFI) in the NIH Guide for Grants and Contracts. The RFI will be announced in the Federal Register and through other media. The USDA and FDA will use communications with their stakeholders to alert them to the RFI as well. All three agencies will carefully consider the responses in preparing a report on actions to be taken by the agencies and the impact on relevant stakeholders.

#### SENATOR CASSIDY

*Question 1.* What types of guidance and regulatory reform are needed to ensure non-pharmacological interventions are better utilized for pain management?

*Question 2.* What are some of the barriers that exist to utilizing physical therapy and other non-pharmacological treatments for pain management?

Answer 1 and 2. There are numerous barriers to integrated pain care that incorporates non-pharmacological treatments for people with chronic pain. The 2011 Institute of Medicine (IOM) Report: *Relieving Pain in America* identified major barriers as institutional, educational, organizational, and reimbursement—related and

noted that the greatest challenges are in the primary care setting where most pain management occurs.

The IOM report considered provider training in pain management across many disciplines to be inadequate, based on national surveys of professional schools' pain curricula. Lack of training coupled with the complexity of pain often results in patients not receiving appropriate referrals for multidisciplinary care despite evidence that non-pharmacological approaches are effective for many pain conditions. Many primary care settings do not have interactions/access to facilities that provide non-pharmacological treatment options. This situation is more acute across vulnerable populations in rural areas and in communities with limited resources where no such options exist. Poor public awareness of pain and treatment options, the stigma associated with pain, and the reliance on pharmacological management, often prevent patient-provider communication of individual treatment needs.

Both providers and payers are concerned that the evidence base for best clinical practice in pain management is weak and so not helpful in determining practice guidelines and coverage policies. For those non-pharmacological treatments with evidence of efficacy, dissemination and implementation of these clinical practices has not been effective in reaching the patients. Until recently there was no broad analysis of published evidence to show what non-pharmacological treatments are effective for different pain conditions. In 2017, AHRQ completed a systematic review of the literature, describing in detail the evidence base for non-pharmacological treatment approaches for five common pain conditions. This comprehensive review is intended to help develop and disseminate practice guidelines. It also provides a resource for payers to structure their coverage policies and processes for integrated pain care.

Many organizational barriers to access to non-pharmacological treatments are driven by current reimbursement policies of public and private insurers. An extensive survey of coverage of pharmacological and non-pharmacological treatment for low back pain by 50 state Medicaid, Medicare, and private payers found inconsistent to no coverage for many non-pharmacological treatments, while most analgesics were universally covered with fewer pre-authorizations, restrictions, and lower co-pays.

Interviews with key informants revealed a relative emphasis among plans on reducing opioid prescribing rather than increasing coverage for non-pharmacological treatments. The study revealed that determination of coverage of pharmacologic and non-pharmacologic therapies are separate process, suggesting that plans do not integrate coverage in the context of multimodal, comprehensive treatment for pain. Only one plan fully integrated non-pharmacological therapies into step therapy requirements for opioid initiation.

Knowledge barriers still exist. Pain is variable, affects people differently, and patient responses to treatment are unique. We lack adequate understanding of pain mechanisms, individual risk factors for who is likely to develop chronic pain, and therefore need further research to guide tailored treatments.

*Question 1.* Dr. Collins, in our hearing you mentioned that Congress had the responsibility to set NIH funding levels for particular institutes. As you know, your agency, working with other parts of the Administration, also has a role in that process by requesting certain funding levels in the President's yearly budget request to Congress.

To what degree do you use your discretionary funding request to increase funding for institutes such as NIDA which are addressing the societal impact of addiction?

*Answer 1.* The annual President's Budget reflects the Administration's fiscal policy goals for the entire Federal Government, and NIH develops its request in close coordination with other divisions within the Department of Health and Human Services and with the Office of Management and Budget. Within that framework, NIH pursues its highest research priorities through strategic investments and careful stewardship of appropriated funds. NIH activities that are considered part of the National Drug Control Budget, which includes the entire NIDA budget and part of the NIAAA budget, receive special attention in a section of the Overview Volume of the NIH congressional Justification.

SENATOR COLLINS

*Question 1.* In 2013, Congress approved the National Pediatric Research Network Act (NPRNA). As you know, the law provides authorization for a nationwide network of research consortia to conduct basic and translational pediatric research. Last year, as part of the 21st Century Cures Act, Congress included language to

drive forward implementation of that network. I have been informed that NIH believes the IDeA States Pediatric Clinical Trials Network constitutes implementation of the NPRNA. Notwithstanding the important merits of the IDeA States program, I have heard concerns as to whether it fulfills the statutory intent of the NPRNA, which is to create a nationwide network of investigator-initiated and multi-institution pediatric research partnerships.

For example, researchers in my State of Utah (and in 26 other states) are not eligible to apply for this particular program because Utah is not an IDeA state. The NPRNA was envisioned as a national network where each consortium would receive funding for shared core research infrastructure for a coordinating central academic center and auxiliary sites, bringing together top experts and patient populations wherever they may be. Proposals for these pediatric research consortia would be reviewed and scored via the NIH peer review process. What actions has the NIH taken to date, and what actions are planned in the coming months, to further implement the NPRNA?

Answer 1. Pediatric research has been and continues to be an NIH priority. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas. In Fiscal Year (FY) 2017, the NIH funded approximately \$4.1 billion in research grants and projects directed specifically at pediatric research, an increase of \$220 million over fiscal year 2016 spending. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the 27 NIH Institutes, Centers, and Offices (ICOs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, all of the ICOs support various aspects of pediatric research, such that the NICHD alone accounts for only 18 percent of the total NIH support for pediatric research. This reflects the breadth of the research portfolio at the NIH dedicated to improving the health of children everywhere.

The NIH intends to meet the goals of the National Pediatric Research Network Act through four networks: the Environmental influences on Child Health Outcomes (ECHO) program IDeA States Pediatric Clinical Trials Network, the Pediatric Trials Network, the Neonatal Research Network, and the Rare Diseases Clinical Research Network.

The IDeA States Pediatric Clinical Trials Network (ISPCTN) provides medically underserved and rural populations with access to state-of-the-art clinical trials, apply findings from relevant pediatric cohort studies to children in IDeA State locations, and build pediatric research capacity at a national level. Funding for this new network also supports professional development of faculty-level researchers and their support teams in the conduct of clinical trials research. The awards are a component of the ECHO Program, which is investigating how exposure to a broad range of environmental factors in early development, from conception through early childhood, influences the health of children and adolescents. It is important to note that the ISPCTN funds research centers in states where there was little to no pediatric research capacity prior to its creation.

ISPCTN consists of multiple institutions arranged in a "hub and spoke" model, with each of its 17 clinical sites in a separate IDeA State and its central Data Coordinating and Operations Center located at the University of Arkansas for Medical Sciences. ISPCTN uses this network model to foster collaboration, coordination, and sharing of resources not only within the Network but also to partner with other NIH networks focused on pediatric biomedical research to increase representation of children from beyond the IDeA States.

The Pediatric Trials Network (PTN) is comprised of over 100 clinical research sites across the United States with over 7,000 children enrolled. The PTN provides evidence for the formulation, dosing, efficacy, and safety of medications and medical devices in infants and children. The PTN conducts pediatric clinical drug trials in a variety of therapeutic areas, including but not limited to cardiovascular diseases, cancer, infectious diseases, gastroenterology, respiratory diseases, neonatology, and medical devices. Current studies include research on the pharmacokinetic and pharmacodynamics properties of antipsychotic drugs in children and adolescents, a study on the effectiveness of sildenafil to decrease the risk of pulmonary arterial hypertension in preterm infants, and research on the pharmacokinetics of methadone to treat opioid withdrawal in children.

The NIH also supports a national network focused on neonatal research. The Neonatal Research Network (NRN) is a collaborative network of neonatal intensive care units across the United States, comprising 18 clinical centers and a data coordinating center. Focused on newborns, particularly extremely low-birth-weight in-

fants, the NRN conducts clinical trials and clinical studies in such areas as sepsis and other infections, bronchopulmonary dysplasia and other lung conditions, and necrotizing enterocolitis, a condition in which the intestines lack oxygen or blood flow.

Finally, the NIH prioritizes research into rare diseases that affect children. The Rare Diseases Clinical Research Network (RDCRN) program, led by the National Center for Advancing Translational Sciences (NCATS) in collaboration with other NIH Institutes, is a model designed to advance medical research on rare diseases. The RDCRN currently includes 100 institutions and clinical sites in 33 states examining over 6,000 children each year. Several of the Rare Diseases Clinical Research Consortia (RDCRC) focus on or include rare diseases that affect children, including brittle bone diseases, mitochondrial diseases, immune deficiencies, Rett syndrome and Rett-related disorders, sterol and isoprenoid conditions, urea cycle disorders, genetic disorders of mucociliary clearance, developmental synaptopathies, and lysosomal storage diseases, among others.

Collectively, these networks support research capacity across the United States to address unmet pediatric research needs. NIH fully expects these networks to continue to expand and will continue to seek out partnerships with all stakeholders and other pediatric research consortia.

#### SENATOR ROBERTS

*Question 1.* In your written testimony you mention efforts underway to “cut the bureaucratic red tape that slows the process of science.” Can you provide more detail on how NIH is working to reduce administrative burdens on medical researchers?

*Answer 1.* For decades, NIH has focused on reducing administrative burden in various ways including but not limited to, leading efforts within the Federal Demonstration Partnership (FDP) and supporting efforts coordinated by the White Houses’ Office of Science and Technology Policy. The NIH Director, Dr. Francis Collins, co-chairs the National Science and Technology Council’s Committee on Science (CoS). Further, NIH co-chairs a CoS interagency working group, called the Research Business Models Working Group, that aims to improve coordination and collaboration among Federal research agencies to streamline requirements for the extramural research community.

In response to the fiscal year 2015 omnibus report language, NIH engaged and actively participated in a collaborative effort to address the issue of administrative burden with the ad hoc committee of the National Academies of Science. This group studied Federal regulations and reporting requirements with specific attention to those directed at research universities. The resulting report, “Optimizing the Nation’s Investment in Academic Research: A New Regulatory Framework for the 21st Century” was issued in two parts. Part I focused on regulatory issues identified as of most pressing concern to the research community, while Part II contains the analysis of topics that adversely affect the Nation’s ability to optimize its investment in academic research.

The report recommended existing Federal policies and processes be harmonized across agencies, such as by using a uniform format for grant proposals and research progress reporting. It also recommended reducing the regulatory burden associated with policies for human subjects’ research, animal care and use, monitoring of sub-recipients, reporting of financial expenditures, and disclosure of financial conflicts of interest. In addition, the Committee recommended that Congress establish the Research Policy Board (RPB), which would serve as a public-private forum for discussions relating to regulations of federally funded research.

The 21st Century Cures Act required research funding agencies modify and harmonize regulations and policies with similar purposes to minimize administrative burden to the greatest extent possible, all while maintaining responsible oversight of federally funded research. Further, the RPB was required to be established to provide Federal Government officials with information on the effects of regulations related to Federal research requirements.

NIH has implemented several of the 21st Century Cures Act provisions, including eliminating Paperwork Reduction Act requirements for scientific studies, and automating the issuance of certificates of confidentiality as a “term and condition of award” for awards involving human subjects so NIH-funded researchers no longer need to request one. Further efforts to streamline applications for clinical trials, effective for due dates on or after January 25, 2018, include a structured data form for human subjects research fields that eliminates duplicate information entries. In

addition, NIH and FDA partnered together to develop a clinical trial protocol template<sup>6</sup> with instructional and example text for NIH-funded investigators to use when writing protocols for phase 2 and 3 clinical trials. NIH developed a simplified application appendix<sup>7</sup> to rectify inequities in peer review that arise from submission of inappropriate or excessive appendix materials.

NIH continues to work with HHS to decrease burden involved in financial conflict of interest reports, reducing audit burden by raising the threshold, waiving the requirement for subrecipient monitoring when the subrecipient is in good standing, and simplifying and harmonizing animal care regulations.

NIH is partnering with ORCID<sup>8</sup> to enable scientists to include additional data fields useful to maintain and update biosketches and CVs across multiple platforms. ORCID is a not-for-profit organization that assigns unique persistent identifiers to researchers that supports automated linkages between researchers and their professional activities with the goal of helping people find information and to simplify reporting and analysis. NIH's eRA Commons, an online interface where signing officials, principal investigators, trainees and post-doctoral fellows at institutions/organizations can access and share administrative information relating to research grants, is establishing a real-time link with ORCID, which allows users to associate ORCID with their eRA account. Further, NIH and other funders are collaborating on the ORCID Reducing Burden and Improving Impact Tracking (ORBIT) project. This effort will expand the ORCID data model beyond publications to data elements typically found on a CV, such as grants, courses taught, presentations, and other research products. To this end, in 2017, NIH developed guidance on how NIH applicants have the option, for applications submitted for due dates of May 25, 2017 and beyond, to cite interim research products such as preprints in applications.

NIH continues to consider ways to address the recommendations to reduce the administrative burden associated with Federal research funding outlined in the NAS report and 21st Century Cures Act. For some of these recommendations, NIH can take action by implementing changes to grant policies.

Because all of the provisions of the 21st Century Cures Act have not been fully implemented, it is too early to determine the effect on research. However, NIH is diligently working with university faculty and research administration staff to ensure that measures implemented by NIH to reduce administrative burden are effective.

*Question 2.* The Office of Management and Budget has a statutory deadline to establish a Research Policy Board to work on this topic. Has NIH been engaged with OMB on this priority?

Answer 2. In 2017, HHS, through NIH, provided technical support to the OMB related to the Research Policy Board (RPB). For additional information regarding the RPB, we refer you to OMB.

*Question 3.* In your testimony, you note that the success rate for applicants being awarded NIH grants is below 20 percent. How, or do, you see that number improving over the next several years as the additional funding from Cures is appropriated to NIH?

Answer 3. NIH would like to see the success rate for competing research project grants increase toward the 30 percent level last seen in fiscal year 2003. The additional funding from Cures is a step in the right direction, assuming that it supplements rather than replaces the regular annual appropriations. The success rate depends on the number of new and competing awards as well as the number of grant applications. NIH's purchasing power has declined by 16 percent since fiscal year 2003, while the number of applications increased by over 50 percent. Our ability to improve the success rate will depend on the total appropriations level going forward. With so many promising biomedical research opportunities available today and expected in the future, we don't anticipate a significant drop in the number of grant applications.

<sup>6</sup> NIH and FDA Release Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials

<sup>7</sup> Updated Appendix Policy Eliminates Clinical Trial-Related Materials for NIH/AHRQ/NIOSH Applications Submitted to Due Dates on or After January 25, 2018

<sup>8</sup> Teaming with ORCID to Reduce Burden and Improve Transparency

## SENATOR WARREN

*Question 1.* Antibiotic resistant bacteria kill approximately 23,000 people each year.<sup>9</sup> According to the CDC, 10 percent of patients believe that have had an allergic reaction to penicillin, however, only 1 percent are actually allergic to penicillin.<sup>10</sup> The misdiagnosis of penicillin allergy can lead to the inappropriate use of broad-spectrum antibiotics and increased antibiotic resistance. A 2014 study of patients with penicillin allergies showed that “testing for penicillin allergy may result in cost savings, improved patient care, and fewer drug-resistant bacteria.”<sup>11</sup>

a. What research has the NIH conducted on penicillin allergy testing?

Answer a. While the NIH is not currently funding research on penicillin allergy testing, it has encouraged the development of research proposals in the broader field of drug allergy through funding initiatives (see response to Question 1b).

b. What opportunities for collaboration exist between the NIH and other Federal agencies to educate patients and providers about penicillin allergy testing and the impact this testing has on antibiotic resistance bacteria?

Answer b. The NIH has encouraged the development of research proposals on drug allergy through the funding initiatives described below. The NIH collaborates with Federal agencies and other partners as appropriate to advance research on drug allergy and welcomes additional opportunities to disseminate research findings to key stakeholders such as scientists, patients, and healthcare providers.

The NIH held a workshop on drug allergy in 2013 that brought together U.S. and international experts in the field of drug allergy as well as representatives from the U.S. Food and Drug Administration (FDA). The NIH collaborated with the FDA to hold a second workshop on drug allergy in 2015. Based on the research agendas developed during these workshops, the NIH developed a drug allergy-related initiative. This effort includes two companion NIH-wide initiatives titled “Serious Adverse Drug Reaction Research” (PAR-16-274 and PAR-16-275) to stimulate new research on drug reactions, including research on drug allergy. In addition to these NIH-wide efforts, research on drug allergy also has been a focus of the NIAID initiative “Asthma and Allergic Diseases Cooperative Research Centers” (AADCRCs; RFA-AI-16-065). The AADCRC program promotes multidisciplinary basic and clinical research on the immunological basis, pathobiology, diagnosis, treatment, and prevention of asthma and allergic diseases.

## SENATOR WHITEHOUSE

*Question 1.* The Recalcitrant Cancer Research Act required the NIH to develop “scientific frameworks” for cancers that have a low 5-year survival rate and cause the death of at least 30,000 Americans each year. The NIH is currently using those frameworks to guide its research priorities related to pancreatic cancer and small cell lung cancer. Has any of the funding Congress provided for the Cancer Moonshot Initiative been directed to research objectives identified by the scientific frameworks?

*Question 2.* The NIH is required to report on the actions taken to carry out the Recalcitrant Cancer Research Act in each biennial (now triennial) report, and is required to report to Congress on the effectiveness of the frameworks within 6 years of their initial development. Do you commit to fulfilling these reporting obligations?

Answer 1 and 2. NIH, through the National Cancer Institute (NCI), commits to fulfilling all remaining requirements of the Recalcitrant Cancer Research Act: to report on actions taken to carry out the Act in each NIH biennial (now triennial) report; to update the Pancreatic Ductal Adenocarcinoma (PDAC) scientific framework and the Small Cell Lung Cancer (SCLC) scientific framework in 2019, 5 years after their initial development; and to provide a one-time report on the effectiveness of the frameworks within 6 years of their initial development.

The PDAC and SCLC scientific frameworks continue to inform NCI research efforts, including the Cancer Moonshot. It is also important to understand that NCI conducts such scientific horizon scanning efforts on an ongoing basis to help advance

<sup>9</sup> “Antibiotic Resistance Threats in the United States, 2013,” Centers for Disease Control and Prevention (online at: <https://www.cdc.gov/drugresistance/threat-report-2013/index.html>). Accessed Dec. 20, 2017.

<sup>10</sup> “Is it Really a Penicillin Allergy?” Centers for Disease Control and Prevention (online at: <https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf>). Accessed Dec. 20, 2017.

<sup>11</sup> Laurie Barclay, “Most Patients Misinformed About Penicillin ‘Allergy’ History,” Medscape (April 3, 2014) (online at: <https://www.medscape.org/viewarticle/821429>).

cancer research in all areas. To identify the most promising ideas from the field, NCI engages in a highly collaborative process that draws upon our external advisory groups and steering committees, the expertise of NCI program leadership, and opportunities to convene expertise via workshops and other collaborations to discuss the State of cancer research in many scientific disciplines, and to consider new opportunities.

Several cross-cutting research efforts supported through the Cancer Moonshot in fiscal year 2017 stand to benefit pancreatic cancer patients and small cell lung cancer patients, these include NCI's Human Cancer Models Initiative and related efforts focusing on cancer models for translational research; the development of new enabling cancer technologies to characterize tumors and test therapies; and enhanced data sharing through a cancer data ecosystem that includes NCI's Genomic Data Commons.<sup>12</sup>

In addition to these cross-cutting efforts, pancreatic cancer was the focus of several Cancer Moonshot awards made in fiscal year 2017 to establish and support a Consortium for Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment.<sup>13</sup> This initiative aims to implement the Cancer Moonshot Blue Ribbon Panel recommendation, considered and approved by the National Cancer Advisory Board (NCAB), to advance cancer immunotherapy translational science, and the specific goal of the Consortium is to understand the interaction between PDAC tumors and their microenvironment to inform the design of new immunotherapy and combination interventions. Consortium awards were made to research teams at Fred Hutchinson, Massachusetts General, Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, MD Anderson, and the University of Michigan.

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RESPONSES BY SCOTT GOTTLIEB TO QUESTIONS FROM SENATOR ALEXANDER, SENATOR MURRAY, SENATOR BALDWIN, SENATOR CASSIDY, SENATOR ROBERTS, SENATOR WARREN, AND SENATOR WHITEHOUSE

SENATOR ALEXANDER

*Question 1.* Diagnostic tests can provide rapid, actionable information for clinicians to help improve the quality of care provided for patients. In many cases, diagnostic tests can be administered outside the traditional laboratory setting and at the point of care, such as physician offices. As part of 21st Century Cures, FDA committed to provide an update of the current FDA guidance on these point of care diagnostic tests, referred to as CLIA waived tests, to ensure it includes appropriate use of comparable performance between a CLIA waived user and a moderately complex laboratory user to meet accuracy requirements.

On November 29, FDA released a draft guidance update to Section V the CLIA waiver guidance, how is the agency working with laboratory and health care professionals to ensure the guidance provides clarity to enable development and availability of CLIA waived tests for patients?

Answer 1. FDA is committed to working closely with stakeholders to ensure the final guidance provides clarity for test developers and promotes the availability of CLIA waived tests. FDA held a webinar on January 8, 2018 covering the draft guidance update to Section V of the CLIA waiver guidance and the related draft guidance to provide recommendations for manufacturers seeking to obtain Dual 510(k) and CLIA Waiver by Application for a new In Vitro Diagnostic (IVD) device and to clarify current FDA thinking. The webinar also provided an additional opportunity for questions and feedback from stakeholders on the draft guidances.

*Question 2.* On November 30, FDA and CMS released a joint announcement approving a next generation sequencing test for use in cancer patients and simultaneously proposing a national coverage determination to ensure Medicare beneficiaries can access the test.

What is FDA doing to work with CMS to ensure this proposal does not limit access to next generation sequencing testing for patients?

Answer 2. FDA is working with additional developers interested in having their oncopanel reviewed by FDA, which could enhance and expand patient access. In addition, on April 13, 2018, the Agency finalized two guidances to drive the efficient development of these novel technologies. The guidances provide recommendations

<sup>12</sup> <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel> / <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding>

<sup>13</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-015.html>

for designing, developing, and validating tests that use the technology, called next generation sequencing<sup>1</sup> (NGS), and will play an important role in the continued advancement of individualized, genetic-based medicine.

The first guidance, Use of Public Human Genetic Variant Data bases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics,<sup>2</sup> describes an approach where test developers may rely on clinical evidence from FDA-recognized public data bases to support clinical claims for their tests and help provide assurance of the accurate clinical evaluation of genomic test results. The guidance describes how product developers can use these data bases to support the clinical validation of NGS tests that they are developing. These public data bases may include resources like ClinGen, which is maintained by the National Institutes of Health (NIH). Using FDA-recognized data bases will provide test developers with an efficient path for marketing clearance or approval of a new test.

The second guidance, Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases,<sup>3</sup> provides recommendations for designing, developing, and validating NGS-based tests used to diagnose individuals with suspected genetic diseases. It describes what FDA would look for in premarket submissions to determine a test's analytical validity, including how well the test detects the presence or absence of a particular genomic change.

Issuance of these final guidances is based on extensive feedback from the public and stakeholders who are developing NGS-based technologies, and the guidances serve as a continuation of FDA's work creating regulatory efficiencies in the development and review of NGS tests. As you note, in 2017, FDA took several actions to streamline the development and review of a variety of genetic-based tests—authorizing a third-party option for conducting reviews NGS tumor profiling tests and making clearance recommendations to FDA,<sup>4</sup> as well as outlining standardized development criteria for carrier screening tests<sup>5</sup> to allow for their marketing without prior agency review. FDA also established such criteria for genetic health risk tests and proposed to allow their marketing after a one-time agency review.

As NGS technologies continue to evolve, FDA remains dedicated to adapting our regulatory review capabilities and leveraging our authorities to the fullest extent in order to make innovative and accurate testing technologies available to patients as efficiently as possible.

The Centers for Medicare and Medicaid Services (CMS) can speak to the specifics of the coverage decision, which was finalized on March 16, 2018.

*Question 3.* Is FDA currently considering similar announcements in other treatment areas?

*Answer 3.* In November 2017, FDA approved Foundation Medicine's FoundationOneCDx (F1CDx) test and on March 16, 2018, CMS finalized a national coverage determination that covers laboratory diagnostic tests for Medicare beneficiaries with recurrent, metastatic, relapsed or refractory, or stage III or IV cancer as part of the FDA-CMS Program for Parallel Review of Medical Devices. Parallel Review is the process through which FDA and CMS conduct overlapping reviews of clinical evidence to shorten the time between FDA approval of a premarket application and CMS granting a national coverage determination for a product. F1CDx is the second IVD to be reviewed through the Parallel Review Program, which was established as a pilot program in 2011. In October 2016, FDA and CMS announced the Parallel Review program would be fully implemented and extended indefinitely.

Sponsors who are interested in Parallel Review for their product can contact the agencies and submit a request that indicates their interest in the program. FDA evaluates and responds individually to each request, in coordination with CMS. If a request is accepted into the program, FDA and CMS concurrently review the clinical study results submitted. It should be noted that FDA and CMS independently review the data to determine whether it meets their respective agency's standards and communicate with the manufacturer during their respective reviews.

If sponsors in other treatment areas request Parallel Review for their device, the agencies will evaluate these requests, and accept them into the program if appro-

<sup>1</sup> <https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/precisionmedicine-medicaldevices/default.htm>.

<sup>2</sup> <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509837.pdf>

<sup>3</sup> <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509838.pdf>

<sup>4</sup> <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585347.htm>.

<sup>5</sup> <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583885.htm>.



appropriate. FDA and CMS anticipate making similar announcements as warranted by product approvals and clearances that go through this program.

*Question 4.* How will FDA work with labs who currently have approval through CLIA programs to maintain the ability to offer their tests following this announcement?

Answer 4. FDA is committed to engaging with any sponsor seeking FDA clearance or approval for their oncopanel test. FDA expects that these tests will be reviewed within the timelines negotiated under MDUFA IV; the Agency met or exceeded its performance goals under MDUFA III.

SENATOR MURRAY

*Question 1.* FDA recently approved Abilify MyCite, which contains “an ingestible sensor embedded in the pill that records that the medication was taken.” We understand that this information can be transferred to an app on patients’ smart phone to track their compliance. While this is exciting technology, it raises important concerns about patient privacy and patient rights, especially given the indication of Abilify for schizophrenia. Congress has clearly directed FDA to assure the patient voice is incorporated in the drug development and review process through provisions in FDASIA, 21st Century Cures, and most recently FDARA, and we seek to understand how the patient voice was considered by FDA during the development and approval of this device.

*Question a.* FDA staff indicated that mental health advocates have pressed the agency for additional options. However, this does not provide an alternative treatment option but rather a way to track the ingestion of a product that was already on the market. Please provide any records to suggest that mental health advocates believe it was important to have this technology as an option for patients.

Answer 1. We agree with the patient and treatment communities that there should be more treatment options for patients with psychiatric disorders, which can encompass a variety of products. We recognize that whether one considers Abilify MyCite to offer a new treatment option depends on the value one puts on its ability to track ingestion of the drug. However, FDA approves products that meet the applicable approval standards found in the Federal Food, Drug, and Cosmetic Act (FD&C Act). With respect to your request for records, we do not have any records of mental health advocates requesting this specific technology as an option for patients.

Abilify without ingestion-tracking technology, as well as generic aripiprazole, remains on the market.

*Question b.* Please provide the Committee with the statement required under Section 569C(b) of the Food Drug and Cosmetic Act (as added by Section 3001 of 21st Century Cures) with regards to Abilify MyCite.

Answer b. The referenced provision only applies to new drug applications (NDAs) and biologics license applications (BLAs) submitted and approved at least 180 days after enactment of 21st Century Cures. Since the NDA for Abilify MyCite, was submitted prior to enactment of the 21st Century Cures Act, this provision does not apply to the Abilify MyCite NDA. However, patient experience data were collected and evaluated as part of FDA’s review of the application. Specifically, the applicant conducted human factors studies that examined how patients used the product.

*Question c.* Please provide the committee information regarding the original device approval for which this drug product is based, including its indications for use.

Answer c. A De Novo Request was granted for the device in 2012 with the following indications for use:

The Proteus Personal Monitor is a miniaturized, wearable data-logger for ambulatory recording of heart rate, activity, body angle relative to gravity, and time-stamped, patient logged events, including events signaled by swallowing the Ingestion Event Marker (IEM) accessory. The Proteus Personal Monitor enables unattended data collection for clinical and research applications. The Proteus Personal Monitor may be used in any instance where quantifiable analysis of event-associated heart rate, activity, and body position is desirable.

*Question d.* How does FDA plan to assess how the drug is used post-market? Are there any planned collaborations with the National Institute of Mental Health, or other organizations to assess how it is being used, if at all, by insurers, employers or others to track patient compliance?

Answer d. FDA reviews safety information and other complaints that are received after approval, as we do with any drug. The Agency’s system of postmarketing surveillance uses multiple mechanisms to assess risk and identify adverse events. FDA

also actively seeks patient engagement and provides a variety of opportunities for patient and caregiver involvement in the Agency's work. To date, FDA has no projects planned to survey how Abilify MyCite is being used to track ingestion.

*Question 2.* While the FDA considers the risks and benefits of a product to treat a specific indication in approval decisions, the agency is, above all else, an agency with the mission of protecting and promoting public health. Consideration of broader public health concerns in product approvals is consistent with this mission, and this practice is now being more widely adopted by the agency in approval decisions for opioid products.

*Question a.* How does FDA determine which drug and device reviews should include a public health assessment?

Answer 2, a. Protecting and promoting the public health is central to the mission of the Food and Drug Administration. As such, public health assessments are part of all aspects of our work including review and approval or clearance of drugs and medical devices, to the extent such assessments are consistent with the statutory criteria applicable to such decisions. Teams of FDA experts, including physicians, statisticians, chemists, pharmacologists, clinicians, engineers, and social scientists conduct unbiased reviews of drugs and devices submitted for approval or clearance that include appropriate consideration of the expected public health impact of such products. As part of the Agency's public health assessment, experts analyze the target condition and available treatments; assess benefits and risks from clinical data; identify strategies for managing risks; and consider patient input and experience. FDA also relies on Advisory Committees to provide independent advice. Committee members include scientific and public health experts—such as physician-researchers and statisticians—and members of the public, including Patient Representatives.

*Question b.* Were public health concerns for the mental health patient community, such as the possibility of forced treatment by insurers, employers, or family members taken into account during the approval process for Abilify MyCite? If not, why not?

Answer b. Yes. In applying the benefit/risk framework to Abilify MyCite, FDA considered public health concerns, patient rights, and ethical issues. Considering these factors, scientific evidence about the product's safety and efficacy, and all other appropriate information, FDA determined that the benefits of Abilify MyCite outweighed its known and potential risks for the intended population.

FDA further determined that addition of the tracking technology did not pose any significant risks. The choice to use Abilify MyCite will be made by the patient in consultation with his or her physician. Patients will work with their physicians to determine whether they want the version of the drug that has the tracking technology, and, if so, whether to grant access to ingestion tracking information to the patient's healthcare provider or caregiver.

This drug/device combination with digital tracking is optional. Abilify without ingestion-tracking technology, as well as generic aripiprazole, remains on the market.

*Question c.* Were public health concerns from the eating disorder community, including individuals with binge eating disorder and bulimia, taken into account during the approval process for the Aspire Assist weight loss device, which allows a user to empty their stomach contents after eating? Were concerns about contributing to the development of these disorders considered? If not, why not?

Answer c. Yes, FDA considered whether devices to treat obesity could contribute to the development of eating disorders and patients were monitored for the development of eating disorders at several time points during the year-long clinical trial.

The AspireAssist device is contraindicated in those with, among other conditions, diagnosed bulimia, diagnosed binge eating disorder, and night eating syndrome. The device design also limits the number of patient uses that are possible between office visits and locks the device once the limit is reached. Patient perspective, benefits of weight loss, risk of adverse events, and the risks of chronic obesity were also among factors FDA considered. In addition, CDRH staff have met with representatives of the eating disorder community (health care professionals and patient representatives from the Binge Eating Disorder Association, National Eating Disorder Association, and Eating Disorders Coalition) to discuss their perspectives about devices intended to treat or manage obesity.

Moreover, FDA has mandated two "condition of approval" studies in addition to postmarket surveillance and reporting required for all medical devices. One study is assessing compliance with AspireAssist therapy and transient weight-loss following the therapy; impact of AspireAssist therapy on eating behavior, incidence, duration and severity of adverse events (in particular, infection and stoma-related

issues); and the effectiveness and safety outcomes after device explant. The second study is an extended follow-up multicenter, single-arm prospective, active surveillance study designed to gather long-term data on the incidence, duration, and severity of adverse events, weight loss, compliance with AspireAssist therapy, impact of AspireAssist therapy on eating behavior and the effectiveness and safety outcomes after device removal.

*Question 3.* Given the proliferation of medical software and app technologies, how many inspections of software developers has FDA performed this year?

*Answer 3.* In 2017, FDA performed 604 inspections of medical device establishments with a profile code description including computer software. This profile code description indicates that the activities performed at the establishment include software development.

*Question 4.* According to FDA public data, FDA has not issued a warning letter to any software firms this year, which means that either all medical apps on the market are approved devices, or fall into categories of enforcement discretion or exemption, or that we don't have a full grasp of all the products on the market. How is FDA assessing currently marketed products to assure that they are compliant with the appropriate regulatory frameworks?

*Answer 4.* In 2017, FDA issued eight warning letters to establishments with a profile code description including computer software: Dentio, Inc.; ELJTechGroup B.V; Magellan Diagnostics, Inc; National Biological Corp; St. Jude Medical Inc.; TeleMed; Unetixs Vascular Inc.; and Video Inc.

FDA's assessment of marketed products occurs partly through ongoing surveillance of the marketplace and, in many cases, patients, consumers, health care providers, and others notifying us of a potential violation of laws or regulations. For products we know are legally marketed, our assessment includes postmarket surveillance and taking enforcement action when needed. Medical device manufacturers as well as other firms involved in the distribution of devices must follow certain requirements and regulations once devices are on the market and FDA ensures compliance with those requirements through reports and inspections.

#### SENATOR BALDWIN

*Question 1.* We need to do more to advance prevention, treatment and detection tools for botulinum neurotoxin poisoning, which presents a significant risk to human health due to its high toxicity, ease of manufacturing, and lack of medical interventions. Development of effective treatments and vaccines for botulinum neurotoxins (BoNTs) is slow despite recent advances in testing methods using cell-based assays. The use of live mice as a so-called animal "bio-assay" for BoNTs has been the primary tool used by researchers and vaccine developers. But, in recent years, many developers are utilizing advanced and effective cell-based assays, which reduce costs and provide significantly less risk for the laboratory workers handling the animals than the legacy mouse assay.

*Question a.* Dr. Gottlieb, what information is the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) providing to researchers and product developers on the use and efficacy of cell-based assays for botulinum neurotoxin(s)?

*Answer 1.* We welcome and encourage sponsors to engage early and proactively with FDA through the appropriate product center. This helps us better understand their prospective product(s), provides a mechanism to discuss and evaluate innovative laboratory tools that may expedite product development, and helps facilitate efficient development programs. We encourage this engagement either in the context of individual applications or by pursuing qualification of these tools, where appropriate, through the process set forth in section 507 of the FD&C Act (as added by section 3011 of the 21st Century Cures Act).

*Answer a.* Early and proactive engagement with FDA provides direction to sponsors, even prior to submission of an Investigational New Drug (IND) application, in regards to the design of preclinical and clinical studies to assess the safety and effectiveness of each product. FDA's feedback throughout all stages of product development is intended to help protect human subjects, facilitate consistent product manufacture, and help ensure that pivotal clinical studies are designed in such a manner that the study results will provide sufficient information to allow an evaluation of the product's safety and effectiveness.

It is the responsibility of the sponsor of a new product to approach FDA with adequate assay development data for each test method it proposes to use during product development. Some sponsors have supported approval of their products utilizing

cell-based assays for routine product testing ( e.g., for potency testing), while others have supported approval using animal-based testing. It is the sponsor's prerogative to decide which type of test method it believes will be best suited for its product and to provide data to support its use. Post-licensure, sponsors have the option to develop replacement test methods should they deem a change appropriate. FDA encourages the use of state-of-the-art innovations, whenever possible. As long as product safety and effectiveness are not compromised, FDA encourages the use of tests that are not animal-based. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will generally consider if such an alternative method could be assessed for equivalency to an animal test method .

FDA will continue to look for opportunities to provide more information to researchers and product developers on all aspects of the drug development process whether through FDA guidance documents, workshops, or individual interactions.

*Question b.* Will FDA include updated information on cell-based assays in the required guidance documents under Section 3011 of the 21st Century Cures Act?

Answer b. As noted above, FDA encourages developers of cell-based assays to engage with the Agency, including by pursuing qualification of these tools, where appropriate, through the process set forth in section 507 of the FD&C Act ( as added by section 3011 of the 21st Century Cures Act (Cures Act)). To that end, the guidance documents that FDA is required to publish under section 301 1 of the Cures Act may be useful to developers of cell-based assays who wish to seek qualification under that process. These guidance documents must address the conceptual framework for qualification of biomarkers, as well as the processes and timeframes associated with the drug development tool qualification process more generally. However, the Agency does not anticipate that the required guidance will address specific tools or technologies such as cell-based assays.

#### SENATOR CASSIDY

*Question 1.* What types of guidance and regulatory reform are needed to ensure non-pharmacological interventions are better utilized for pain management?

Answer 1. FDA continues to support education for all opioid analgesic prescribers. The Agency has recently revised and updated the FDA Blueprint, "Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain." FDA recently announced plans to expand REMS to require the manufacturers of immediate-release (IR) and extended-release and long-acting (ER/LA) opioid analgesics, intended for outpatient use, to make training available to opioid prescribers and other healthcare professionals involved in the management of patients with pain. The manufacturers will meet this requirement by providing educational grants to accredited continuing education (CE) providers who offer the training. The training will be based on the FDA Blueprint which contains core educational messages for health care providers involved in the treatment and monitoring of patients with pain. It also includes more information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The Blueprint section on non-pharmacologic approaches (copied below) encourages health care providers (HCPs) to be knowledgeable about the range of treatment options available and reminds HCPs that not all non-pharmacologic options have the same strength of evidence to support their utility in the management of pain.

#### II. GENERAL PRINCIPLES OF NON-PHARMACOLOGIC APPROACHES

Pain can arise from a wide variety of causes. There are a number of non-pharmacologic and self-management treatment options that have been found to be effective alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain. Examples include, but are not limited to, psychological, physical rehabilitative, and surgical approaches, complementary therapies, and use of approved/cleared medical devices for pain management. HCPs should be knowledgeable about the range of treatment options available, the types of pain that may be responsive to those options, and when they should be used as part of a multidisciplinary approach to pain management. HCPs should also be aware that not all non-pharmacologic options have the same strength of evidence to support their utility in the management of pain, and some may be more applicable for some conditions than others.

In the last 5 years, FDA has approved at least 10 novel devices to aid in the management of chronic or intractable pain. These devices are appropriately regulated to assure both safety and effectiveness. FDA is exploring whether additional guidance may be helpful in communicating our thinking about how to design robust clinical studies and assess clinical data from a variety of sources, including real world evidence, for pain management devices.

*Question 2.* What are some of the barriers that exist to utilizing physical therapy and other non-pharmacological treatments for pain management?

Answer 2. Based on our experience in premarket evaluation of pain management devices, we believe a barrier to increased use by health care providers and patients of such devices is the limited availability of data about safety and effectiveness of new pain devices. More robust effectiveness data, including evidence from postmarket studies, could help remove the barriers to use of new pain devices by clinicians and patients.

*Question 3.* The effectiveness of a new CNS drug is notoriously difficult to measure, because there are often not readily available and well-understood biomarkers or patient-reported outcomes/endpoints. Section 3011 of the 21st Century Cures Act requires the Secretary to establish an improved process for the qualification of drug development tools, upon the request of a drug manufacturer, for use in supporting FDA approval of a new drug or biologic. The Secretary must develop criteria for accepting a qualification package, and may prioritize the development of new tools based on disease prevalence, the lack of available treatments, and public health priorities, among others.

*Question a.* How will you utilize these provisions to close the gap for CNS drugs, through developing an expedited process to qualify biomarkers and drug development tools?

Answer 3. For years, FDA has operated a qualification process for drug development tools (DDTs), including biomarkers and clinical outcome assessments. Section 3011 of the Cures Act builds upon these efforts, establishing a new framework governing the DDT qualification process. The new provision directs FDA to develop a regulatory process to facilitate timely and consistent review of DDT qualification submissions and publicly disseminate information about DDTs at certain stages of review and following a qualification determination. This authority allows the Agency to work with submitters as they develop or refine a DDT that, once qualified, can be used across drug or biologic development programs for a particular context of use. We hope that this will facilitate the development of drugs and biologics in many areas where there are patients with serious diseases and unmet needs, including CNS drugs. In addition to pursuing the qualification of DDTs, we strongly encourage sponsors and drug developers to contact the Division of Neurology Products in CDER or Office of Tissues and Advanced Therapies in CBER so that we can provide targeted advice specific to their drug development programs.

*Question b.* Are the qualification of new tools for development of CNS drugs a high priority, particularly given the looming burden of Alzheimer's Disease facing our country and the fact that CNS drugs continually lag in development compared to drugs for other therapeutic areas?

Answer b. FDA recognizes the urgent need for new medical treatments for many serious neurological conditions, including Alzheimer's Disease. The Agency is working hard to further drug development in this area, including issuing draft guidance for industry in February 2018, entitled *Early Alzheimer's Disease: Developing Drugs for Treatment*. Moving forward, FDA is eager to work with sponsors who are interested in developing DDTs for Alzheimer's or other neurological treatments.

#### SENATOR ROBERTS

*Question 1.* One new requirement under the Cures Act is for manufacturers of an investigational drug to make its policies on evaluating and responding to compassionate use requests publicly available. Can you provide an update on how effective this new requirement has been? Are patients getting the information they need and is the process becoming easier to navigate?

Answer 1. FDA supports the goal of making more information available to patients and physicians; however, the Agency does not generally receive data regarding compliance with FD&C Act section 561A, as established by the 21st Century Cures Act. FDA also does not generally receive data regarding patient/physician experience or their satisfaction with information they obtain from manufacturers relative to expanded access (EA). Therefore, we are unable to provide an assessment regarding the effectiveness of this provision.

We do note, however, that FDA worked with the Reagan Udall Foundation (RUF) as they developed their Expanded Access Navigator, which became publicly available in July 2017. The RUF Navigator's express purpose is to help patients and physicians navigate the EA request process. The Expanded Access Navigator, among other things, includes a directory where companies can submit public links to their expanded access policies, criteria used by companies to determine whether to make a drug available through expanded access, and company/manufacture contact information. In addition, FDA has updated its EA guidance with information about company responsibilities under FD&C Act section 561A. FDA also continues to update its own EA website with new information intended to bring clarity and transparency to the EA process.

*Question 2.* There are many treatments that have additional uses that are medically accepted, that doctors can prescribe for their patients, and that the Federal Government will even pay for-but FDA prohibits the manufacturers, who know the most about their products, from discussing those uses under most circumstances. During your confirmation, you commit to working with FDA's staff to get up to speed on the agency's latest thinking and actions on these matters, and providing clarity to manufacturers, payers, providers, and patients about acceptable truthful and non-misleading communications related to clinical data not already incorporated in a label. What steps do you anticipate the FDA taking in this area and what is the timeline for such actions?

Answer 2. FDA is engaged in a comprehensive review of its regulations and policies on medical product communications to ensure that our implementation of FDA's legal authorities best protects and promotes the public health in light of ongoing scientific and legal developments.

In addition, in January 2017, FDA issued two separate draft guidances that help provide clarity for medical product companies, as well as other interested parties, on FDA's current thinking and recommendations for a few different types of communications about medical products. The first draft guidance addressed common questions regarding firms' dissemination of health care economic information (HCEI) about approved drugs to payers, formulary committees, and similar entities; and provided recommendations for sharing certain information about investigational products (drugs and devices) with these entities. Comments on this guidance raised the issues of expanding the HCEI recommendations to devices (an issue on which FDA specifically requested comments) and of expanding the recommendations on sharing certain information to cover information about unapproved uses of approved products, in addition to other important issues.

The second draft guidance provides answers to common questions regarding firms' communication of information about the approved or cleared uses of their products that is not contained in, but is consistent with, the FDA-required labeling for the product. The guidance provides details about the types of information that could be considered consistent with the FDA-required labeling, and FDA's recommendations for how firms can communicate this information in a truthful and non-misleading way. Comments on this guidance have asked for greater clarity around how FDA determines if a product communication is consistent with the FDA-required labeling, as well as requested additional recommendations for presenting such information in a truthful and non-misleading manner.

FDA currently is working to issue final guidances.

*Question 3.* In 2011, FDA issued an Advisory on glass lamellae formation in certain injectable drugs. The Advisory noted at the time that ". . . there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic and other vascular events." Does FDA have plans to update the Advisory and if so, what is the expected timeframe for doing so?

Answer 3. The advisory issued in 2011 outlined the conditions associated with a higher incidence of the formation of glass lamellae, such as glass vials manufactured under higher heat by tubing process, drug solutions at high pH and with certain buffers, storage temperature and shelf life, and terminal sterilization. The advisory also provided literature references and included recommended actions to help prevent the formation of glass lamellae. In addition to the advisory, which drew attention to the issue after several recalls due to formation of glass lamellae, the Agency also provided the recommendations regarding glass lamellae in a Question & Answer guidance for industry on current good manufacturing practices (CGMP).<sup>6</sup> Drug

<sup>6</sup> See Question 11. [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124780.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124780.htm).

manufacturers can still follow these recommendations to help prevent formation of lamellae.

FDA has met with manufacturers to address design and manufacturing for glass products intended for injectable drugs and appreciates industry's efforts to address quality issues that may cause safety problems associated with use of glass products in the manufacture of pharmaceuticals. FDA plans to meet the Omnibus requirement to report on this matter to the Committee.

*Question 4.* The Director of the Drug Center's Office of Compliance recently stated that one out of every four inspections of compounders in last year resulted in a recall. How is FDA working to address this and ensure patient confidence in compounded medications?

Answer 4. Compounded drugs present a greater risk to patients than approved drugs. For example, because they are not FDA-approved, compounded drugs are not reviewed by the Agency before they are marketed for safety, effectiveness, and quality. In addition, drug products compounded in accordance with certain conditions set forth in section 503A of the FD&C Act are statutorily exempt from current good manufacturing practice requirements, the quality standard that applies to conventional drug manufacturers. Because compounded drugs are subject to a lower regulatory standard than FDA-approved drugs, the Agency cannot "ensure patient confidence in compounded medications." However, reducing the risks associated with poor quality compounded drugs that could lead to serious patient harm is a priority for FDA, and the Agency continues to dedicate significant resources toward this effort.

By way of background, the 2012 outbreak of fungal meningitis, resulting from a pharmacy that shipped contaminated compounded drugs throughout the country, led to more than 750 cases of illness and 60 deaths in 20 states. The tragic proportions of this outbreak were mainly attributable to the company's large-scale, multistate distribution of an injectable drug intended to be sterile that had been prepared under inappropriate conditions. This outbreak, combined with FDA's continued concerns based on monitoring pharmacy compounding, underscored the need for improvement in compounding practices. It also highlighted the need for more robust oversight of compounders, close Federal and State collaboration, and a clear legal framework that would provide for compounding to meet patients' medical needs, while also providing FDA with tools to address unlawful practices that threaten public health.

Since enactment of the Drug Quality and Security Act (DQSA), a statute that Congress passed in 2013 after the fungal meningitis outbreak, FDA has prioritized policy development to implement the law, State and stakeholder collaboration, and oversight efforts. With respect to oversight, since enactment of the DQSA and as of January 2018, FDA has conducted nearly 500 inspections of compounders, issued more than 180 warning letters advising compounders of significant violations of Federal law, issued more than 70 letters referring inspectional findings to State regulatory agencies, overseen more than 150 recalls involving compounded drugs, and worked with the Department of Justice on multiple civil and criminal enforcement actions.

As FDA has engaged in these inspection and enforcement efforts, it has observed increased compliance with certain provisions of Federal law applicable to compounding. However, the Agency still encounters serious problems, some resulting in recalls of drug products due to substandard conditions that could lead to contamination or other quality concerns. Further, because the vast majority of the thousands of state-licensed pharmacies and physicians that compound drugs in the United States are not required to register with the Agency and are routinely overseen by the states and not by FDA, the Agency might not become aware of a problem, such as substandard production conditions, until after it has resulted in harm to patients.

Any entity that produces drugs, including compounded drugs, is responsible for ensuring that it complies with Federal laws such as those concerning production standards and drug quality. FDA intends to continue to engage in robust oversight of compounding, in collaboration with its State partners, and to take action when it identifies violations of Federal law.

SENATOR WARREN

#### **shortages of blood pressure medication**

*Question 1.* I have heard from multiple constituents in Massachusetts who report facing shortages of blood pressure medication, including Atenolol. One constituent

reported needing to switch medications as a result of not being able to obtain her blood pressure medication at the pharmacy. Another reported checking multiple pharmacies and being told that there was no medication available. News reports indicate that this shortage is affecting individuals across the country, not just in Massachusetts.<sup>7</sup>

Four drug manufacturers—Mylan Pharmaceuticals, Sandoz, Teva Pharmaceuticals, and Zydus Pharmaceuticals—have reported shortages of Atenolol tablets to the FDA.<sup>8</sup> Based on the most recent information reported to the FDA, Zydus Pharmaceuticals is now able to supply current customer demand and has increased capacity to support additional demand, while other manufacturers reported limited supply or backorders.

*Question a.* What steps is the FDA currently taking to resolve shortages of Atenolol?

Answer 1., a. As of August 1, 2018, all four of these manufacturers of atenolol tablets have product available, except for Sandoz, which has limited supply. Please reference our webpage for updated supply information.<sup>9</sup>

*Question b.* Has the FDA received reports of shortages of generic blood-pressure medications in addition to Atenolol?

Answer b. As of August 1, 2018, we have not received reports of shortages of generic blood-pressure medications in addition to atenolol.

#### SENATOR WHITEHOUSE

*Question 1.* Please describe the FDA's approach in its Software Pre-certification Pilot Program. If the FDA decides to exempt certain software developers from pre-market review, what types of post-market controls does the agency envision in this space to protect consumer safety?

Answer 1. For the American people to see the full benefits of digital health products, FDA is using the Software Pre-Certification Pilot Program to explore a possible regulatory framework that accommodates the distinctive nature of digital health technology, its clinical promise, and its compressed iteration cycle.

Under this possible framework, for an organization to be pre-certified, the organization would demonstrate that it has a culture of quality and organizational excellence, providing assurance that the organization produces high quality, safe, and effective products. In some cases, software that is a medical device (referred to as "SaMD," for "software as a medical device") developed by a pre-certified organization may undergo streamlined premarket review; in such cases, the pre-certified organization would submit less information in a premarket application than they would today. In other cases, a pre-certified organization may begin marketing SaMD without a premarket submission and immediately begin post-market data collection. We expect pre-certified organizations to collect robust real-world data to monitor the safety and effectiveness of devices in the field and for FDA to have access to this data. FDA expects to retain its existing postmarket enforcement tools and to use them as necessary to protect public health. Aspects of this program may require additional statutory authority.

FDA looks forward to continuing to collaborate with the pilot participants and the public to develop the Software Pre-Certification Program. FDA intends for the program, when finalized, to promote the public health by supporting the innovation of high quality, safe, and effective digital health devices.

[Whereupon, at 12 p.m., the hearing was adjourned.]



<sup>7</sup> Sylvia Perez, "Doctors, Patients Concerned over Shortage of Blood Pressure Drug 'Atenolol,'" Fox 32 Chicago (November 10, 2017) (online at: <http://www.ox32chicago.com/news/localdoctors-patients-concerned-over-shortage-of-blood-pressure-drug-atenolol>). Larry Husten, "Generic Atenolol in Short Supply," *MedPage Today* (August 10, 2017) (online at: <https://www.medpagetoday.com/cardiology/cardiobrief/67185>).

<sup>8</sup> "Atenolol Tablets," Current and Resolved Shortages and Discontinuations Reported to the FDA (July 26, 2017) (online at: <https://www.accessdata.fda.gov/scripts/drugshortages/dsp-ActiveIngredientDetails.cfm-AI=Atenol/percent20Tablets&st=c&tab=tabs-1>).

<sup>9</sup> <https://www.accessdata.fda.gov/scripts/drugshortages/dsp-ActiveIngredientDetails.cfm-AI=Atenol/percent20Tablets&st=c&tab=tabs-1>