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**CONTINUING AMERICA'S LEADERSHIP IN MEDICAL
INNOVATION FOR PATIENTS**

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

FIRST SESSION

ON

EXAMINING CONTINUING AMERICA'S LEADERSHIP IN MEDICAL
INNOVATION FOR PATIENTS

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MARCH 10, 2015
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CONTINUING AMERICA'S LEADERSHIP IN MEDICAL INNOVATION FOR PATIENTS

TUESDAY, MARCH 10, 2015

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

The committee met, pursuant to notice, at 10:04 a.m., in room SD-430, Dirksen Senate Office Building, Hon. Lamar Alexander, chairman of the committee, presiding.

Present: Senators Alexander, Murray, Burr, Isakson, Collins, Cassidy, Mikulski, Casey, Franken, Bennet, Whitehouse, Baldwin, and Warren.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order. Senator Murray and I will each have an opening statement. We'll then introduce our witnesses, and after the witnesses, Senators will have 5 minutes of questions. I have really been looking forward to this day. This is a very important hearing.

Dr. Collins, I thank you for coming.

Dr. Hamburg, I thank you for coming, especially because that caused a change in plans.

We don't have two people who know more about what we're talking about than the two of you. This is an opportunity for us to discuss that.

Let me see if I can put this in some sort of context. This is a busy committee. In the last Congress, Senator Harkin used to point out that we completed 25 pieces of legislation which became law, and Senator Murray and I are working well together.

There are three major items that we intend to focus on in the next 2 years, among all the others. No. 1 is fixing No Child Left Behind, and we're working well together toward that and hope to have a markup on that after the recess.

Second, we're working on simplifying and reauthorizing the Federal Government's supervision of higher education in America. We had a hearing on that recently, and it had an impressive report. Senator Mikulski, Senator Burr, Senator Bennet, and I had asked about simplifying regulations. That will be second.

The third topic is to deal with this exciting new era of medicine that we have and take a look at what we can do as a Congress, working with the President, to reduce the cost and the amount of time it takes to go from discovery of a medicine or a treatment or

a medical device and take it all the way through to the medicine cabinet or the doctor's office.

We know important work has been done in the Congress on that not so long ago. We have an opportunity this year to make whatever contribution there is to make, and it's an area that we ought to succeed in, because there's not really a political partisanship about this issue.

In fact, the House of Representatives is moving on a parallel track on something they call 21st Century Cures. President Obama is extremely interested in precision medicine. I attended his announcement of that interest at the White House recently along with Dr. Collins and Dr. Hamburg. I've talked with him about it and with Secretary Burwell.

Suffice it to say that I believe every single member of this committee is interested in identifying what we can do to make it easier to move those drugs, treatments, and devices from discovery all the way through to the medicine cabinet. We're not just talking about moving it through the FDA. Sometimes it takes 2, 4, 6, 10, 12 years to get to the FDA's front door. So we're not just talking about the FDA. We're talking about the whole range of issues there.

Dr. Collins has described it this way. He wrote in 2013,

“Drugs exist for only about 250 of the more than 4,400 conditions with defined molecular causes. It takes far too long and far too much money to get a new drug into our medicine cabinets. This is an old problem that cries out for new and creative solutions.”

Since Dr. Collins wrote that, the number of conditions with defined molecular causes has increased to more than 5,400. The number of new drugs approved has not kept pace with these discoveries. Dr. Hamburg, who is here today, has said that we are left relying on the 20th century approaches for the review, approval, and oversight of the treatments and cures of the 21st century.

President Obama, in his announcement of the new Precision Medicine Initiative, said 21st century business will rely on American science, technology, research, and development. The President said,

“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine, one that delivers the right treatment at the right time.”

In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable.

He introduced at that White House announcement a 27-year-old young man whose cystic fibrosis has been cured because he was 1 of 4 percent of the sufferers with that disease caused by a mutated gene for which there is now a drug. The legislation Senator Bennet and Senator Burr worked on may have helped to contribute to that opportunity. This is a discussion that can affect nearly every American and one which we're going to take very seriously.

Senator Burr and I issued a white paper that we had been working on for some time that focused on the issues that we thought the committee ought to identify, and we've submitted that to Senator Murray and to the rest of the members of the committee for their consideration on: costing too much to bring medical products

through the discovery process and development process taking too long, whether FDA's responsibilities include unrelated activities to what the focus should be, the disparity in scientific knowledge at the FDA and the fast pace of biomedical innovation. Those are some of the issues that we focused on.

What we hope to learn today from two distinguished leaders of our government is exactly what we should be focusing on. We don't want to waste our time, and we can't do everything. If this train is moving through the station in the next 12 months, and if our goal is to help get from discovery to the medicine cabinet or the doctor's office, what are the two or three things that we ought to spend our time on?

I believe we can do that, working together. We're excited about it. It's a chance for your agencies and the rest of the government to let us help you get the obstacles out of the way that might be in the way of your getting your job done. Some of them relate to money. Some don't. Some relate just to the pile-up of administrative regulations.

At our hearing on higher education, Chancellor Zeppos from Vanderbilt talked about the fact that he hired a Boston consulting group to assess the cost of rules and regulations to operate Vanderbilt University for 1 year, and the answer was \$150 million, \$11,000 onto every student's tuition at the university.

There's a whole range of things. I'm looking forward to this. I thank you, Dr. Collins, and I thank you, Dr. Hamburg.

I'll now turn to Senator Murray, and we'll then turn to the witnesses.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Chairman Alexander.

Dr. Collins, Dr. Hamburg, it's great to have you both here. I have a lot of appreciation for the work that you do to encourage innovation and improve health and well-being.

Dr. Hamburg, as you step down from your role at FDA, I especially want to thank you for your many, many years of service, and we're all very grateful for your leadership.

Thank you very much from all of us.

I am very pleased to be working with Chairman Alexander and other members of the committee on ways that we can continue to advance biomedical innovation for patients. I believe that we are at a truly fascinating moment in medical innovation right now. We increasingly have the ability to move away from a one-size-fits-all model of treatment and instead treat patients according to their unique characteristics.

We've seen enormous growth in life sciences as a source of economic strength and job creation. My home State of Washington is a great example. Life sciences are the fifth largest employment sector in my State, and it's growing. These are good jobs in an industry with global reach, and our country needs more of them.

It is critical that we secure and build on the United States' leadership in medical innovation. To do this, I believe Congress has to look at how we ramp up investment in the kind of research and development that helps drive this private sector growth. That's

something I will be very interested in exploring as part of our bipartisan efforts in the coming weeks and months.

Dr. Collins, I know that you are very concerned about the impact of sequestration and what it has done to NIH, and I am, as well. I hope that we can talk about that today as well. I'm also eager to hear more about the many efforts at NIH to ensure the United States remains the global leader in biomedical research and discovery.

The FDA drug and device approval process is another topic that I know will receive a lot of focus.

Dr. Hamburg, you recently announced that in 2014, the FDA approved 51 new drugs, which is the most in almost 20 years. You should be very proud of what that means for patients and families across the country. I look forward to hearing from you today about ways that we can build on that progress.

Another priority I will be focused on is the needs of women and young children in the research, development, and approval process. When we looked at the FDA approval process back in 2005, Senator Kennedy reminded us that when patients open up their medicine cabinet, they deserve every assurance that the medicines they take are safe and effective, and that is just as true today. As our conversations about advancing medical innovation move forward, I will be guided by his vision of upholding that assurance.

In the weeks and months ahead, I hope we can reach an agreement on policies that help get safe and effective treatments to patients more quickly. That would be good for our economy and could really make all the difference for so many families we represent.

Thank you again to our witnesses for being here today.

Thank you, Chairman Alexander, for holding this hearing.

The CHAIRMAN. Thank you, Senator Murray.

We have a good attendance already of Senators. I would say that we have formed a working group of the staff, a single working group, on this subject for the purpose of identifying how we will proceed. After this hearing, in the next few weeks, the working group and Senator Murray and I will sit down and talk about how we can have a bipartisan process and take into account and focus our efforts in a way that gets a result. In that, we'll be aware of what the House is doing, and we'll work with Secretary Burwell and with the President, especially on their Precision Medicine Initiative.

I would ask each witness to summarize, if you can, in about 10 minutes, your testimony so that Senators will have a chance to have a conversation with you. I thank you both for coming.

Dr. Collins first—thank you—Director of the National Institutes of Health, the largest supporter of biomedical research in the world. He has been Director of NIH since 2009. He is known for his leadership of the international human genome project which led the first completely sequenced human genome in 2003.

Next we'll hear from Dr. Hamburg. She is Commissioner of the Food and Drug Administration. According to our staff, 25 cents of every consumer dollar that's spent in the United States, you regulate when you regulate prescription drugs, medical devices, food and tobacco products.

Dr. Hamburg has been in this role for 6 years.

I'm glad she's here, and I'm glad she's here because she is retiring, and she has this wealth of knowledge accumulated over the last 6 years. I especially asked her to come for that purpose because I knew the committee would want to hear from her.

Dr. Hamburg, thank you very much for your service to our country. Even though you may be retired, we hope you'll continue to advise us, especially during this next year as we work through these issues. And I thank Senator Murray and Senator Mikulski for keeping me straight on my comments.

Dr. Collins.

**STATEMENT OF FRANCIS COLLINS, M.D., Ph.D., DIRECTOR,
NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD**

Dr. COLLINS. Good morning, Chairman Alexander, Ranking Member Murray, members of this important committee. It is an honor to appear before you today alongside my friend and colleague, FDA Commissioner Peggy Hamburg. Our agencies have much to gain by working together, and we have been doing so and we're committed to that effort. In fact, Peggy and I spent a productive 3 hours just yesterday afternoon, along with senior leaders from both of our agencies who make up the NIH FDA leadership council, discussing a wide range of projects we are working on together.

I'd like, on behalf of the NIH, our employees, grantees, and patient community, to thank members of this committee for your continued support and for holding this bipartisan hearing today. I appreciate the opportunity to discuss how we as a nation can drive innovation through Federal investments in scientific research.

Breakthroughs generated by NIH research—and I'm going to show you a few visuals here, if you can see the screen—are behind many of the gains our country has enjoyed in health and longevity.

[Slides Shown.]

For example, over the past 60 years, deaths from cardiovascular disease have fallen by more than 70 percent. Meanwhile, cancer death rates have been dropping about 1 percent annually for the last 20 years. Likewise, HIV/AIDS treatments have greatly extended lives, and prevention strategies are enabling us to envision the first AIDS-free generation.

Today, I want to share with you a few of the many promising opportunities for biomedical research innovation. I can assure you the potential of scientific research has never been brighter than it is today. NIH remains strongly committed to basic science, fundamental research that serves as the foundation for discoveries that have long made America the world leader in biomedicine and accounts for no less than 145 Nobel prizes that have been awarded to our scientists that we support through NIH grants and through our intramural program.

One exciting example in basic science is the BRAIN initiative. This bold, multiagency, multiyear effort is enabling development of innovative technologies to provide a clearer, more dynamic picture of how individual brain cells and neural circuits interact in time and space. This initiative will ultimately give us the tools for major advances in brain diseases, from Alzheimer's and autism to schizophrenia and traumatic brain injury.

NIH is also innovating in translational science, where basic science findings are developed into clinical benefits. Let me give you a few examples. Recent advances in technology have led to the discovery of more than 1,000 risk factors for disease. Drug development is a terribly difficult and failure-prone business. A major reason for failures is that scientists often just don't know how to choose the right pathways to target for the next generation of drugs that they want to develop.

With this in mind, we were excited just a year ago to launch the Accelerating Medicines Partnership, or AMP. This is an unprecedented, precompetitive, public-private partnership using cutting edge scientific approaches to choose the most promising targets for therapeutic intervention. Besides NIH, AMP partners include, importantly, the FDA, 10 biopharmaceutical firms, and a number of nonprofits, including patient advocacy groups.

Initially, AMP is focusing on three disease areas that are ripe for discovery of the next generation of drug therapies: Alzheimer's disease; Type 2 diabetes; and the autoimmune disorders, rheumatoid arthritis and lupus. Through this innovative and collaborative approach, we believe we can learn how to treat and cure disease faster, and we can do it together across this whole ecosystem.

NIH is also working to streamline the therapeutic development pipeline through an effort at our newest center, NCATS. More than 30 percent of promising medications fail in human clinical trials because they are found to have unacceptable toxicity despite promising pre-clinical studies. Could we do better?

While the Tissue Chip for Drug Screening Initiative is developing 3-D human tissue biochips that model the structure and function of organs, such as the lung, liver, and heart, these organoid chips—and you can see the heart chip there is actually beating in real time because the cells that are on that chip are cardiac muscle cells that are synchronized to beat just as they would if they were in a heart. These give us the opportunity to mimic complex functions of the human body without putting humans at risk, enabling scientists to predict more accurately how effective a therapeutic candidate would be in clinical studies, eliminating toxic or ineffective drugs earlier in the development process.

Scientific advances are also accelerating progress toward a new era of precision medicine. Historically, doctors have been forced to base their recommendations for treatment on the expected response of the average patient. Recent advances, including the plummeting cost of DNA sequencing, now make possible a more precise approach to disease management and prevention that takes into account individual differences in genes, environment, and lifestyle.

With this in mind, NIH is thrilled to take a lead role in the multiagency Precision Medicine Initiative that you all have already mentioned in the opening statements and which we at NIH are very excited about. In the near term, this initiative will focus on cancer. To accelerate efforts, this project will support research aimed at understanding why cancer has developed drug resistance, using noninvasive methods to track therapeutic responses to so-called liquid biopsies, and exploring new treatments including combination therapies targeted to the genetic profiles of a wide range of adult and pediatric cancers.

As a longer-term and very bold goal of this initiative, NIH will launch a national research cohort of 1 million or more volunteers who will play an active role in how their genetic and environmental information is used to prevent and manage a broad array of diseases. A project of this magnitude will lay the groundwork for new prevention strategies and novel therapeutics. There's no better time than now to embark on this enterprise to revolutionize medicine and move this precise personal approach into everyday clinical practice.

In closing, to make this clear in terms of its impact on human health, allow me to share a story that highlights the early promise of precision medicine. When Maki Inada was diagnosed with stage 3-B adenocarcinoma of the lung in 2008, it was completely unexpected. She was 36 years old, never smoked a day in her life, and yet her tumor was very large, as shown on this film, 7 centimeters, with a very low likelihood of survival beyond a year or two.

As Maki began the recommended standard chemotherapy, her doctors, who were ahead of their time in precision medicine, suspected she might have a particular mutation in a gene called the epidermal growth factor receptor, or EGFR. Genetic testing confirmed their hunch. Maki was prescribed Tarceva, a drug that precisely blocks EGFR's signal.

After 3 months of treatment, Maki's large tumor shrunk dramatically, as you can see. This was followed by surgery to remove cancerous tissue plus retreatment with Tarceva. Today, 7 years after her diagnosis, her doctors can detect no signs of cancer. What's more, Maki has now completed a triathlon, landed her dream job as a biology professor at Ithaca College, and welcomed a healthy baby girl.

Maki is the face of scientific innovation made possible by sustained investments in biomedical research. With your support, we can realize the vision of accelerating discovery across the vast landscape of biomedicine, from basic science inquiry to more precise personalized approaches to treatments and cures.

Thank you, Mr. Chairman. My colleagues and I welcome your questions.

[The prepared statement of Dr. Collins follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D.

Good morning, Chairman Alexander, Ranking Member Murray, and distinguished members of the committee. I am Francis S. Collins, M.D., Ph.D., and I am the Director of the National Institutes of Health (NIH).

It is an honor to appear before you today, alongside my dedicated colleague, Dr. Hamburg, to discuss how we, as a Nation, can drive innovation through Federal investments in scientific research. On behalf of NIH, our employees, grantees, and patient community, I want to thank members of this committee for your continued support and for holding this hearing today.

As the Nation's premier biomedical research agency, NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems, and to apply that knowledge to enhance human health, lengthen life, and reduce illness and disability. All of us at NIH believe passionately in this mission, and are dedicated to the pursuit of innovative strategies to achieve it.

NIH has been advancing our understanding of health and disease for more than a century. Scientific and technological breakthroughs generated by NIH-supported research are behind many of the improvements our country has enjoyed in public health. For example, our Nation has gained about 1 year of longevity every 6 years

since 1990.¹ A child born today can look forward to an average lifespan of about 78 years—nearly three decades longer than a baby born in 1900. Deaths from cardiovascular disease have been reduced by more than 70 percent in the past 60 years. HIV/AIDS treatment and prevention may now enable us to envision the first AIDS-free generation since the virus emerged more than 30 years ago. Cancer death rates have been dropping about 1 percent annually for the past 15 years. These are extraordinary strides—but we aim to go much further.

Today, I want to share with you a few of the many promising opportunities for biomedical research innovation. I can assure you that the future of scientific research has never been brighter.

Scientific advances are accelerating progress toward a new era of personalized medicine. Historically, physicians have had to make recommendations about disease prevention and treatment based on the expected response of the average patient. This one-size-fits-all approach works for some patients and some conditions, but not others. Technology developments, along with plummeting costs of DNA sequencing, now make it possible to develop an innovative approach to treatment that accounts for individual differences in patients' genes, environments, and lifestyles. To this end, through the President's Precision Medicine Initiative announced in January, NIH and our colleagues at FDA and the Office of the National Coordinator for Health Information and Technology will work together on this bold new research effort to revolutionize how we improve health and treat disease. A near term goal of the President's Precision Medicine Initiative focuses on cancer; cancer research has been leading the way in precision medicine by defining the driver mutations in individual tumors and using this information to design the ideal therapy for each patient. To accelerate the pace of discovery, this initiative seeks to expand current cancer genomics research to understand the development of resistance to targeted therapy, to apply non-invasive methods to track patients' responses to treatment, and to explore the efficacy of new drug combinations targeted to specific tumor mutations.

As a longer term goal of this initiative, NIH also plans to launch a national research cohort of one million or more volunteers, who will volunteer to play an active role in how their genetic and environmental information is used for the prevention of illness and management of a wide array of chronic diseases. This venture will pioneer a new model for doing science that emphasizes engaged participants, technologically advanced collection of many different data types, responsible data sharing, and privacy protection. A project of this magnitude will lay the foundation for a myriad of new prevention strategies and novel therapeutics. There's no better time than now to embark on this ambitious new enterprise to revolutionize medicine and generate the scientific evidence necessary to move this personal approach into everyday clinical practice.

NIH also is supporting the basic science that is fundamental to scientific advances in biomedicine. One way we are working to unravel life's mysteries is with the President's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative announced in 2013. NIH is partnering with colleagues at the National Science Foundation, the Defense Advanced Research Projects Agency (DARPA), the Intelligence Advanced Research Projects Activity (IARPA), and the Food and Drug Administration (FDA), in this effort to revolutionize our understanding of the most complicated biological structure in the known universe, the human brain. This multiyear initiative will produce a clearer, more dynamic picture of how individual cells and neural circuits interact in both time and space. By measuring activity at the scale of neural networks in living organisms, we can begin to decode sensory experience and, potentially, even memory, emotion, thought, and consciousness. Ultimately, the technologies developed within the BRAIN Initiative may help reveal the underlying pathology in a vast array of brain disorders and provide new therapeutic avenues to prevent, treat, and cure neurological and psychiatric conditions such as Alzheimer's disease, autism, schizophrenia, traumatic brain injury, and addiction.

NIH is also innovating in translational science—where basic science findings are developed into clinical benefits. Let me give you a few examples.

Recent advances in genomics, proteomics, imaging, and other technologies have led to the discovery of more than a thousand risk factors for disease—biological insights that ought to hold promise as targets for drugs. Drug development is a terribly difficult and failure-prone business. To the dismay of researchers, drug companies, and patients, the vast majority of drugs entering the development pipeline never emerge as patient-ready therapies. The most distressing failures occur when a drug is found to be ineffective in the later stages of development—in Phase II or

¹http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf.

Phase III clinical studies—after years of work and millions of dollars have already been spent. A major reason for such failures is that scientists often don't know how to choose the right clinical pathway to target. If a drug is aimed at the wrong target, it won't work against the disease it was intended to treat.

With this in mind, we were thrilled to launch the Accelerating Medicines Partnership (AMP) last year. This unprecedented public-private partnership is using cutting-edge scientific approaches to sift through a long list of potential therapeutic targets and biomarkers, and choose those most promising for therapeutic intervention. Besides NIH, AMP partners include FDA, 10 biopharmaceutical firms, and a number of non-profits, including patient advocacy groups.

Accelerating Medicines Partnership (AMP)

Government	Industry	Non-Profit Organizations
NIH	AbbVie	Alzheimer's Association
FDA	Biogen Idec	American Diabetes Association
	Bristol-Myers Squibb	Arthritis Foundation
	GlaxoSmithKline	Foundation for the NIH
	Johnson & Johnson	Geoffrey Beene Foundation
	Lilly	Juvenile Diabetes Research Foundations
	Merck	Lupus Foundation of America
	Pfizer	Lupus Research Institute/Alliance for Lupus Research
	Sanofi	PhRMA
	Takeda	Rheumatology Research Foundation
		USAagainstAlzheimer's

This pre-competitive partnership is focusing initially on three disease areas that are ripe for discovery: Alzheimer's disease, type 2 diabetes, and the autoimmune disorders, lupus and rheumatoid arthritis. Costs are shared equally between NIH and the participating companies, and all data is openly shared. Through this truly innovative and collaborative approach, we believe we can learn how to treat and cure disease faster.

NIH is also working to streamline the therapeutic development pipeline through efforts at the National Center for Advancing Translational Sciences (NCATS). One example is the Tissue Chip for Drug Screening Initiative, a collaboration with DARPA and FDA, with a goal of improving the process for predicting whether drugs will be safe in humans.

More than 30 percent of promising medications fail in human clinical trials because they are found to have unacceptable toxicity, despite promising pre-clinical studies in animal models. The Tissue Chip for Drug Screening Initiative is developing 3-D human tissue biochips that model the structure and function of human organs, such as the lung, liver and heart. These chips are then combined into an integrated system that can mimic complex functions of the human body. This technology should enable scientists to predict more accurately how effective a therapeutic candidate would be in clinical studies, eliminating toxic and/or ineffective drugs earlier in the development process. Tissue chips will benefit basic and clinical researchers throughout the entire pharmaceutical and biotechnology sector.

Another way NCATS is working to advance therapeutics development is through the Discovering New Therapeutic Uses for Existing Molecules program. This collaborative approach partners NIH researchers with industry to provide opportunities to reposition and repurpose drugs for new indications. By using agents that already have cleared several key steps in the development process, scientists nationwide have a strong starting point to contribute their unique expertise and accelerate the pace of therapeutics development. This approach utilizes crowd-sourcing to identify the most promising repurposing opportunities, avoiding research duplication and reducing the time and money required to determine if these well-developed agents can be used to treat other medical conditions.

Today, I have provided you with a brief overview of NIH's past successes and continuing commitment to basic, translational, and clinical research. Our nation has never witnessed a time of greater promise in biomedicine, and it is important for the United States to continue to lead in this effort. With your support, we can anticipate a future of accelerating discovery across NIH's broad research landscape, from fundamental scientific inquiry to a new era of personalized approaches to medical treatments.

This concludes my testimony, Mr. Chairman. I look forward to your questions.

The CHAIRMAN. Thank you, Dr. Collins.

Dr. Hamburg.

STATEMENT OF MARGARET A. HAMBURG, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. HAMBURG. Thank you, Mr. Chairman and members of the committee. I'm very pleased to be here today to discuss our shared goal of speeding innovative treatments to patients, and FDA looks forward to working with you on this important effort.

As you have noted, this will be my last appearance before the committee, as I am stepping down. I want to thank you for your support over the years and our constructive engagement with this committee to advance FDA's public health mission.

I came to the agency at a time of considerable uncertainty and change in the biomedical product industry, a time when dramatic advances in science and technology, some that my colleague, Dr. Collins, just outlined, demanded new models and approaches. In turn, we took a very serious look at our role in advancing biomedical product innovation to ensure that we would be a gateway, not a barrier, to the delivery of better, safer, and more effective treatments and cures.

In fact, this has been a high priority for me throughout my tenure, and I'm very pleased that, as Senator Murray noted, last year we approved the most new drugs in almost 20 years and more orphan drugs than ever before, and 41 percent of these new approvals were first-in-class products, resulting in a breathtaking array of truly innovative new therapies for patients. Today, FDA approves drugs faster, on average, than all other advanced nations, 40 days faster than Japan, 70 days faster than Canada, and 174 days faster than Europe.

FDA has made substantial improvement in the efficiency of medical device reviews as well. Moreover, we've accomplished this while remaining the gold standard around the world for safety and effectiveness. Yet despite these successes, too many diseases still await treatments and cures. Serious public health needs, such as treatments for Alzheimer's disease, are not being met, and rising R&D expenditures are not matched by a proportionate discovery of new treatments.

In this context, I want to address concerns raised by some that FDA regulation is the principal obstacle to the development of innovative treatments and suggestions that FDA's authorities and procedures must be fundamentally restructured. As a physician, I know that if you incorrectly diagnose a patient's condition, the treatment that you'll prescribe is unlikely to work. Unless we correctly diagnose why cures are still lacking for many diseases, we're unlikely to find the solutions that will actually deliver those cures. Let me give you three examples of misconceptions.

First is the incorrect but commonly repeated assertion that FDA's approval of new drugs lags behind other countries. The reality is starkly different. Over 75 percent of the new drugs approved by Japan, EU, Canada, Australia, Switzerland, and FDA between 2009 to 2013 were approved first by the FDA, according to a recent report by the British-based Centre for Innovation in Regu-

latory Science. The result is that Americans are, in fact, far more likely to get first access to new medicine.

Second, FDA is said to be rigid and inflexible in its approach to requesting and using data for approval of a new drug. In fact, FDA's clinical trial requirements have been steadily increasing in flexibility. Forty-five percent of new drugs are approved based on a surrogate end point. One-third are approved on the basis of a single clinical trial.

Last year, we used expedited approval processes for more drugs than ever before, about 66 percent. Thanks in part to the new authority that you gave us in FDASIA, 74 drugs have received the new breakthrough designation.

My final example is the concern that investment into biotechnology has dropped precipitously in the United States and that the FDA is to blame. In the words of the National Venture Capital Association, biotechnology investment dollars rose 29 percent in 2014 to \$6 billion, placing it as the second largest investment sector for the year in terms of dollars invested. Jonathan Leff, a leading biotechnology investor affiliated with NVCA, said that one of the two reasons for the increased investment in biotechnology is the improved regulatory climate in recent years at FDA.

I cite these examples to suggest not that the world of biomedical research and product development is all fine, but to urge that we start with the right diagnosis. We do not want solutions based on inaccurate diagnoses. I caution against solutions that seek to lower the safety and effectiveness standards for approval of the medical products on which Americans rely.

Remember that the great leaps forward in evidence-based medicine over the last 50 years have come in part because of the high standards for product approval that Congress put in place after a series of disasters involving unsafe and ineffective medical products. Those standards have also boosted the confidence that Americans place in medical products and that the world places in the American biomedical product industry.

Together, we can build on the progress that has been made in recent years to further advance biomedical science and improve the lives of patients. There are some areas from the FDA perspective that I believe we can all agree need to be improved.

First, patients are uniquely positioned to inform medical product development. Treatments can better meet their needs if we can capture science-based, disease-specific patient input to incorporate in the development and review process.

Second, more attention needs to be given to the development of biomarkers and surrogate end points. These can help scientists identify and target successful medical treatments and shorten drug development times, as Dr. Collins was noting in his remarks. FDA has accepted hundreds of biomarkers and surrogates, such as blood pressure changes, blood sugar reduction, and tumor shrinkage.

Yet biomarkers are still lacking for many diseases, such as Alzheimer's. The biggest obstacle is that scientists do not sufficiently understand the causes of Alzheimer's and other diseases to identify drug targets or identify which patients will benefit from certain drugs. To solve this problem, we must support the establishment

of strong public-private partnerships bringing the best minds together to develop the science that we need.

Third, real-world data provides a vital tool to monitor medical products in use in the marketplace. FDA's Sentinel initiative with more than 170 million lives is one of the largest uses of big data in healthcare and proving vital for monitoring safety and emerging safety concerns. The science of using big data to establish product effectiveness is still in its infancy. Real progress demands that we develop the methodologies needed to harness the promise of real-world data.

And fourth, FDA and industry agree that the agency must be able to attract and retain talented scientists to review cutting edge products. We look forward to working with you to improve our ability to hire and retain these experts.

Let me close by underscoring that speeding innovation while maintaining standards for safety and efficacy serves patients well, supports the needs of our healthcare system, and has enabled the medical product industry in this country to thrive. I thank you for your support for our efforts at FDA, the work that you're going to be doing going forward to advance that work, and the work of all of our colleagues in the biomedical research community so that we can deliver on the promise of science for patients.

Thank you.

[The prepared statement of Dr. Hamburg follows:]

PREPARED STATEMENT OF MARGARET A. HAMBURG, M.D.

INTRODUCTION

Mr. Chairman and members of the committee, I am Dr. Margaret Hamburg, Commissioner of Food and Drugs at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss discovery and development of innovative medical products. My FDA colleagues and I appreciate the committee's interest in advancing legislation to support our shared goal of speeding delivery of innovative, safe, and effective treatments and cures to patients who need them. We look forward to working with you on this effort.

FDA has helped make America's biomedical industry the global leader

Over the past century, remarkable biomedical discoveries have led to the development of medical products responsible for rescuing millions of patients from devastating diseases that previously had led to loss of life or severe reductions in quality of life. The evolution of modern medicine is a story of tremendous hope, learning, and achievement—and one that we all fervently wish to build upon. I am proud of the role that FDA has played in helping these discoveries become safe and effective treatments for patients.

America has long been at the forefront of biomedical discovery. Decades of taxpayer investments in biomedical research, including a focused investment in cancer research, launched in the 1970s, produced fundamental scientific advancements. Significant investments by U.S. pharmaceutical and biotechnology companies, along with the work of NIH-funded investigators across the country, have helped to translate these insights into innovative medical products for patients. FDA oversight of product approvals has built public trust in the safety and efficacy of new drugs and devices and confidence in America's biomedical industry. Major improvements in public health resulted and vital industries flourished. As FDA, Congress, and stakeholders pursue opportunities that provide the most promise for continued development, it is critical that we maintain safety and efficacy of products on which patients and physicians depend.

Public health crises led Congress to establish standards for safety and effectiveness

It is important to recognize that innovative medical products will only save lives if they work properly. As a result of strong standards for medical product approval,

our citizens now depend upon FDA to ensure that the drugs and devices they rely on are safe and effective.

Concerns about the safety and effectiveness of medical products are deeply rooted in our history. In the 19th Century, enterprising traveling salesmen hawked questionable medical products. When newspapers gained widespread circulation, sellers of medical products became leading advertisers of cure-alls containing unlabeled ingredients such as alcohol and narcotics. Eventually, Congress responded by giving FDA authority to review new drugs for safety before they could be marketed.

In 1961, reports started to surface connecting thalidomide, which was widely prescribed in other countries to treat morning sickness during pregnancy, to severe birth defects. Thousands of children in Europe were born with severe birth defects. In response to the public uproar, in 1962, Congress enacted the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Thanks to these new amendments, manufacturers had to prove that a drug was not only safe, but also effective. Approvals had to be based on sound science. Companies had to monitor safety reports that emerged in the post-market and adhere to good manufacturing practices that would lead to consistently safe products. The amendments not only benefited patients, they helped industry by raising scientific standards that ushered in today's sophisticated, science-based life sciences industry.

As we seek to accelerate medical product development, it is essential to take care to maintain those critical aspects of the FD&C Act that ensure the safety and efficacy of these products. History has shown that allowing inadequately tested drugs and devices on the market can cause significant harm to patients, both because of unexpected dangers and, in many cases, because patients may use ineffective products when effective alternatives exist.

FDA has dramatically accelerated access to innovative medical products

This past calendar year, FDA approved 51 novel drugs and biologics, the most in almost 20 years. Today, FDA's average drug review times are consistently faster than other advanced regulatory agencies around the world, providing Americans earlier access to new, innovative drugs than patients in any other country.

In achieving these outcomes, FDA has maintained its commitment to high standards to protect the public health, while also exercising regulatory flexibility in order to help promote medical product development. This flexibility, along with FDA's work to collaborate with industry, has helped reduce product development and review times. As a result, Americans are seeing more products being approved, and in many cases, they have access earlier than patients anywhere else in the world.

FDA routinely works closely with sponsors to facilitate flexible approaches to drug development. One example is FDA's engagement with sponsors to expedite drug development under the breakthrough therapy program. We have also worked with sponsors on the use of surrogate endpoints, non-traditional trial designs, and other available tools to expedite the development of products to treat both common and rare diseases. In fact, more than one-third (69) of the new drug applications approved by the Center for Drug Evaluation and Research (CDER) from 2008 through 2013 were approved on the basis of one human study and supporting evidence. This included 167 novel drugs, some with multiple indications (for a total of 184 new indications). Almost two-thirds (112) have characteristics of a flexible development program and/or engaged in one or more of FDA's expedited development programs (fast track, breakthrough, accelerated approval, priority review), without undermining or diminishing FDA's commitment to a strong safety and effectiveness standard. These many innovative and flexible approaches underscore FDA's commitment to making drugs that are shown to be safe and effective available as rapidly as possible.

Early and frequent communication between sponsors and FDA is significantly reducing overall drug development times. For instance, an analysis of 184 new drug applications approved from 2008–13 concluded that the median clinical development time for drugs that were the subject of a Pre-IND or "early" meeting was 1.4 years faster than drugs without such meetings. Similarly, drug development was reduced by more than a year for companies that sought an End-of-Phase I meeting with FDA, compared to companies that did not request such meetings; and companies that had End-of-Phase II meetings with FDA had higher first-cycle approval rates than those that did not. This analysis includes drugs that did not qualify for an expedited development program.

For devices, FDA's Center for Devices and Radiological Health (CDRH) is focusing on improving investigational device exemption (IDE) submissions to allow earlier and more efficient clinical study enrollment for devices. CDRH has reduced, by 34 percent, the number of IDEs requiring more than two cycles to full approval. These improvements resulted in reducing by over half the median time to full-study ap-

proval. From 2011 to 2014, the median number of days to full IDE approval has decreased from 442 to only 101, cutting the time it takes to bring a new medical device to market by nearly a full year. In addition, improvements to the *de novo* program have resulted in a 70 percent reduction in the average total time to decision for these submissions.

As a result of these improvements, patients are able to receive important treatments sooner. Today, 76 percent of the new drugs approved by Japan, the European Union (EU) and FDA from 2009 to 2013 were approved first by FDA, according to a report released in May by the British-based Centre for Innovation in Regulatory Science.¹

In addition to earlier access to innovative products, patients are also seeing substantial numbers of new treatment options on the market. Of the 51 new molecular entities and new biological products approved by FDA in 2014, 17 new approvals are “first-in-class” therapies, which represent new approaches in the treatment of disease. The greatest number of new drugs approved for “orphan” diseases, since Congress enacted the Orphan Drug Act over 30 years ago, also was seen in 2014. These approvals represent important advances for patients who may have limited treatment options available. Among CDER’s 2014 approvals are treatments for cancer, hepatitis C, and type-2 diabetes, as well. CBER approved many important biological products in 2014, including a groundbreaking vaccine for meningitis B and a vaccine to prevent certain cancers and other diseases caused by a broader range of Human Papillomaviruses.

There are even more opportunities to accelerate medical product development

While tremendous progress has been made thus far, it is important that FDA, Congress, and stakeholders continue working to promote medical product development. In order to ensure that we are promoting the development of products that work properly, it is important that advances are grounded in science. Where there are gaps in scientific understanding, stakeholders can work together to address these gaps so that the public remains confident in the safety and efficacy of products on the market and to ensure that investments in research and development are more likely to have meaningful results.

I would like to share FDA’s thoughts on some of the most promising areas that we believe could truly reach our common goal of speeding delivery of innovative, safe, and effective products to American patients, focusing primarily on transformation of the early stages of drug development and increased efficiency of drug testing and manufacturing. Opportunities to achieve these priorities include: promoting precision medicine; encouraging collaboration and data sharing among scientists; incorporating patient perspectives and experiences; bridging gaps in the science of biomarkers; streamlining clinical trials; modernizing drug manufacturing; obtaining the best experts to help accelerate cures; and reducing administrative burdens and duplication.

Advancing precision medicine

Advances in a variety of fields, including genomics and systems biology, are beginning to produce highly tailored medical treatments based on unique patient characteristics. “Targeted drug development” is a growing area of drug discovery. It is the identification of patients for inclusion/exclusion either in the pivotal studies supporting approval or for the drug’s use in the labeled indication based on a genetic test, biomarker, or susceptibility test (e.g., bacterial resistance, tumor genetic mutation). These treatments are specifically targeted to treat patients who are most likely to respond, or more safely receive, the medication based on specific tests. In the early 1990s, only 5 percent of FDA’s new drug approvals were for targeted therapies. Twenty years later, that number had risen to a quarter of new approvals, and in 2013, approximately 45 percent of FDA’s approvals were for targeted therapies.

President Obama recently announced a Precision Medicine Initiative to advance biomedical understanding by leveraging genomic advances, health information technologies, and new methods of analyzing large volumes of data. As part of that effort, FDA has been reviewing the current regulatory landscape involving next generation sequencing (NGS) as the technology moves rapidly from research to clinical practice. With NGS technology, a single test potentially can be employed to identify thousands—even millions—of genetic variants carried by a single individual. To get the dialog started, FDA published a preliminary discussion paper in late December that posed a series of questions about how to best ensure that tests are not only accurate and reliable, but are available for patients as soon as possible. Public comment is

¹“New Drug Approvals in ICH Countries, 2004–2013,” Centre for Innovation in Regulatory Science, R&D Briefing 54, 2014.

essential, so FDA opened a public docket and held a public meeting on NGS technology on February 20, 2015. As part of the President's Precision Medicine initiative, FDA will develop a new approach for evaluating NGS technologies to facilitate the generation of knowledge about which genetic changes are important to patient care and foster innovation in genetic sequencing technology, while ensuring that the tests are accurate and reliable.

Utilizing real-world observational data

Real-world observational data provides a vital tool to monitor medical product safety and identify and further evaluate concerns. With appropriate privacy protections, leveraging large databases containing patient EHRs, disease-specific registries, and claims data has resulted in significant advances in our understanding of health and disease, provided novel and sometimes surprising insights into potential relationships between health-related factors and outcomes, and provided important product safety data. FDA is currently querying large, diverse health care data for product safety through its Sentinel Initiative and exploring opportunities to expand the use of real-world observational data to optimize the performance of medical products.

Although there is reason to believe that in the appropriate setting these data may be helpful in providing information on the effectiveness of marketed products, such as for new uses of approved products to support label expansion, many experts in the field agree that more work is needed to make these data operational for and directly applicable to regulatory purposes. We should move quickly to further develop methodologies needed to better understand and harness the promise of real-world observational data for regulatory purposes.

Incorporating patient perspectives

Patients are uniquely positioned to inform medical product development with firsthand experience gained from living with a disease, including their use of available therapies to treat their conditions. In Prescription Drug User Fee Act (PDUFA) V, FDA committed to a more systematic and expansive approach to obtaining patient perspectives through a Patient-Focused Drug Development Initiative. FDA has, so far, held 11 public meetings on specific disease areas and gleaned much valuable insight from patients. Important patient-focused work is also already underway through the Medical Device Innovation Consortium (MDIC). MDIC is developing a framework for incorporating patient preferences into the device development and assessment process, and compiling a catalog of methods for collecting patient-preference information that can be used to develop, design, and market devices that meet the needs of patients. One recent example, highlighting the impact of patient perspectives, was the decision to approve a device to treat obesity. The decision to approve the device was based in part on the data from a study that showed a substantial portion of obese patients would accept the risks associated with a surgically implanted device, if they lost a sufficient number of pounds.

We believe that more can be learned and applied by engaging in a transparent, multi-stakeholder approach, potentially through public-private partnerships, that identifies sound and rigorous methods to capture science-based, disease-specific patient input in an analytically meaningful and useful form that can be incorporated directly into drug and medical device development and review processes. This should include capturing information on the natural history of diseases, including identifying and measuring aspects that matter most to patients. Developing guidance to enable patient groups to become active participants in this process and to help industry incorporate appropriate methods in drug development programs also will move the field forward.

Bridging gaps in the science of biomarkers

FDA believes that accelerating the development of reliable biomarkers is essential to advancing important new therapies. FDA already accepts the use of hundreds of biomarkers for a variety of purposes throughout drug development, such as proof-of-concept, diagnosis of disease, enrichment of trials with patients most likely to respond, and as surrogate endpoints that can support accelerated or traditional drug approval. For example, 45 percent of drugs were approved by FDA on the basis of a surrogate endpoint between 2010 and 2012. There remain, however, many diseases such as Alzheimer's disease for which disease-specific biomarkers have not yet been developed, or shown to be reliable for use in the regulatory review process. When we do not understand the disease pathways, biomarkers appearing to be linked to disease progression can fail because they are not, in fact, in the causal pathway for the disease. A wide range of stakeholders is necessary to achieve meaningful progress in developing additional biomarkers that can be used by the scientific community. Important work is already underway through the National Insti-

tutes of Health (NIH), the Biomarkers Consortium in which FDA participates, and the Critical Path Institute.

The principal barrier to biomarker development is the lack of scientific understanding about the causes and biochemical pathways of many diseases. Continued public and private investment in biomedical research is key to filling this knowledge gap and to improving understanding of how to show whether a biomarker is clinically meaningful. Collaboration among NIH, FDA, academia, industry, and patient groups can lead to development of standards of evidence for using biomarkers for regulatory decisions.

Leveraging clinical trial networks

The time and expense associated with designing and conducting clinical trials is one of the most significant limiting factors to drug and device development. Widespread use of clinical trial networks and master protocols could dramatically improve clinical trial efficiency—and create a new drug and device development paradigm that benefits both patients and industry. The recently initiated Lung Cancer Master Protocol (Lung-MAP) is an excellent example. A master protocol creates a single clinical trial infrastructure to test many drugs at the same time. In the case of Lung-MAP, patients are assigned to one of five different drugs being simultaneously tested, based on the results of genomic profiling to screen for alterations in more than 200 cancer-related genes. Additional drugs can be added, or dropped, as appropriate, over time. FDA is highly supportive of the use of master protocols, and we are working with key stakeholders to advance their use.

Modernizing drug manufacturing

Advances in pharmaceutical manufacturing technology provide new opportunities to lower costs, limit drug shortages, and reduce supply chain vulnerabilities—and reinvigorate U.S. pharmaceutical manufacturing. A promising example is the new technology that enables forms of “continuous manufacturing” to produce a finished drug product in a continuous stream, as opposed to traditional methods that involve a series of sequential and discrete “unit operations,” such as milling, mixing, and granulation. Unlike traditional manufacturing, which can take close to a year from start to finish, continuous manufacturing could take only a few days, increase equipment utilization rates up to 95 percent, and dramatically reduce the risk of production failure and negative environmental impacts. Continuous manufacturing could also reduce the likelihood of drug shortages. FDA has been working for over a decade to stimulate modernization of U.S. drug manufacturing, but more work is needed, including supporting academic research in this area and expanding opportunities for collaboration, possibly through public-private partnerships or consortia.

Hiring and retaining highly qualified experts

In order to achieve its mission in a complex, global, and rapidly evolving scientific arena, FDA and industry agree: the Agency must be able to attract, recruit, and retain talented leaders, physicians, scientists, and other experts to effectively review cutting-edge products and conduct post-market surveillance activities. Delays in bringing selected candidates on board may prompt highly qualified experts to pursue opportunities elsewhere.

Allowing use of central Institutional Review Boards (IRB)

The FD&C Act mandates review of a clinical trial on a device by a “local” IRB, or by FDA in rare circumstances, although there is no comparable requirement for drug trials. This can require review of multi-site studies by many different IRBs, and each IRB may require the study sponsor to meet different, sometimes inconsistent requirements for study approval, increasing the length and cost of trials. Studies have shown that the use of a central IRB for multi-site drug studies can significantly improve efficiency, without undermining trial participants’ protections. A modification of the FD&C Act to bring IRB review of device studies in line with drug studies would accomplish the goal of greater efficiency, without sacrificing oversight.

CONCLUSION

I am incredibly proud of the progress that FDA has made during my tenure to speed medical products to patients. I look forward to working with Congress to accelerate product development more while continuing to ensure that American families can rely on the safety and effectiveness of products on the market.

The CHAIRMAN. Thank you, Dr. Hamburg.

We'll now begin a round of 5-minute questions. I'll start. I only have two questions. I have a short one, which I hope I'll get a short response from Dr. Collins, so each of you will have a chance to answer the second question.

The first one is this. The National Academies have done a couple of studies that show that 42 percent of an investigator's time is spent on administrative tasks. The taxpayer spends about \$30 billion through NIH. Eighty percent of that goes into research. In a conversation they had of National Academies said that about 10 percent would be a reasonable amount of time for an investigator, although it would vary depending upon the investigation.

What are the opportunities for reducing that 42 percent down more toward 10 or 12 or 15 percent to save money so that we could have more multiyear investigations? Are there things that we could do to change the law to make that easier for you to do?

Dr. COLLINS. Thank you for the question, Senator. We, too, are very concerned about the idea that investigators are spending 42 percent of their time dealing with administrative matters instead of directly engaged in research, and we're part of the support of that survey, which showed that number has not really changed from 2005 to 2012. We are undertaking a number of things that we have the ability to do to try to limit the amount of administrative oversight, but not all of that falls within our purview. Some of it comes from other directions. Some of it is from the universities themselves.

Things that we have done are to standardize the biographical sketch, the CV, that individuals have to provide when they apply for a grant. That actually turns out to be a substantial assistance.

Something we're in the middle of, where perhaps some help could be offered, is a revision of how to interpret the common rule that oversees the research involving human subjects, which has not gone through a revision in 20 years and which does not currently take account of the risk involved in study and applies a great deal of oversight to some studies that are truly low risk as if they were, in fact, invasive surgical procedures.

The CHAIRMAN. Dr. Collins, may I interrupt in this way? Would you be willing to work with us to identify what those things are, specifically, so that during this next several months, we can—we need to make changes in the law that can help with that, because I want to ask you and Dr. Hamburg this question and—

Dr. COLLINS. Yes.

The CHAIRMAN [continuing]. We don't want to waste our time in the next year, and we can't do everything. Could you say now and then, if you want to submit it later in addition to your statement—what are the one or two or three things that we should focus on in order to make the greatest contribution to the goal of moving medicines, devices, and treatments from discovery to the medicine cabinet, as you put it, or to the doctor's office—each of you?

Dr. COLLINS. Senator, I appreciate that question, and I have a long list, and I'd very much look forward to talking with you at a greater opportunity—

The CHAIRMAN. We'll do that.

Dr. COLLINS. If you want me to name two, one which sounds pedestrian but is an incredibly vexing situation and terribly wasteful

of scientists' time is the current, very rigorous oversight of attendance of scientists at scientific meetings. This applies to both NIH and FDA.

We're currently spending about \$16 million and using hundreds of employees to go through a process which, as far as I can say, has relatively little, if any, added value, all of this triggered by some misadventures by other agencies who convened conferences in places like Las Vegas, for which we are all now paying a price. Scientists going to conferences is a critical part of how we move things forward, how new ideas emerge, and it is very much being inhibited by this very heavy-handed oversight. We could much benefit from your help there.

The second one, I would say—NSF and the Department of Energy and their scientific budgeting that happens every year—they're allowed to carry funds over into a second year. We are not. We come up to the end of September, oftentimes with money that we need to spend or it goes away. If we had the opportunity to carry that over, it wouldn't cost another dime. We could be more flexible in how we spend the taxpayers' money.

The CHAIRMAN. Thank you, Dr. Collins.

Dr. Hamburg.

Dr. HAMBURG. Thank you. I certainly agree with what Dr. Collins said. Are you looking specifically for administrative issues or broader?

The CHAIRMAN. I want to make sure we don't waste our time and that we focus on getting a result. One or two things that—whatever you think.

Dr. HAMBURG. OK. Let me step to a slightly higher level in terms of what I think are two critical and related needs in terms of being able to advance FDA's activities and, in fact, support biomedical research and product development.

One is that I do believe we need to invest more money in regulatory science that develops the knowledge and the tools and approaches and strategies that really enable us to assess in an effective and efficient way the safety, efficacy, quality, and performance of a product. It's been an under-appreciated, under-developed, and under-invested-in area of our overall biomedical product enterprise.

It's proving to be really essential as we are trying to take that last set of steps from research and development into a product that will really make a difference in people's lives. We've laid out an important and exciting research agenda, and we've done work with NIH in this domain.

The other area is to recognize that FDA and our scientists have a huge amount to contribute to the overall process of product development, as well as our important responsibility for review, and, certainly, for us to be able to engage in a consistent way earlier as research plans are being shaped so that the right studies are done so that the return on investment of moneys in research all along the way are really driving toward a product that works.

The CHAIRMAN. Thank you very much.

Senator Murray.

Senator MURRAY. Thank you very much.

Dr. Hamburg, before I go to broader topics, I want to ask you about the recent outbreaks of drug-resistant bacterial infections

that are associated with the use of the special medical scopes known as duodenoscopes. One of the largest outbreaks was in my home State of Washington. There were 32 patients infected, and although it's not clear what caused their deaths, 11 have died.

FDA was supposed to have been regulating these scopes. Can you explain how this could have happened and what actions FDA has taken?

Dr. HAMBURG. The duodenoscopes are very important medical devices that serve a critical role in patient care and diagnosing and treating a series of important problems, and they are, in fact, used in more than 500,000 procedures a year in this country, usually with great benefit to the patients. The duodenoscope allows an approach that is less invasive than open surgery and, overall, has less attendant risks to the patient's health and safety.

Over time, we saw isolated cases of problems in terms of infection in duodenoscopes and we would investigate those, and they were always associated with some lapse in the disinfection protocols. In late 2013, we learned for the first time of some outbreaks unfortunately involving an antibiotic-resistant strain of bacteria where, on investigation, it seemed as though all of the procedures for disinfection had been followed.

After that, we began to work closely with our colleagues at the CDC, with the healthcare provider community, and with the companies making these to try to understand what are some intrinsic design challenges in order to enable this scope to do its job, where it has to kind of twist around and has what's called an elevator mechanism.

We are actively engaged in trying to come up with better strategies for disinfection and recommendations to increase the margin of safety. We're going to be holding an advisory committee meeting. We're working with stakeholders——

Senator MURRAY. Can you commit to a full FDA review to me so we can understand——

Dr. HAMBURG. Sure.

Senator MURRAY [continuing]. How this happened and protect against it happening? Because I am deeply concerned about it.

Dr. HAMBURG. As are we, and we are very actively engaged. A lot of activities are going to be happening moving forward as we continue to try to strengthen the safety of patients and improve what are very important medical devices for care.

Senator MURRAY. I appreciate that.

On a broader issue, Dr. Collins, the United States has always been a global leader in biomedical research and innovation. Today, as you and I both know, sequestration really threatens that leadership, and it's critical that we build on the bipartisan budget deal that I reached with Congressman Ryan last year that helped roll back those cuts from sequestration. We are just about to enter another budget process.

Can you explain to all of us today how sequester impacted research at NIH?

Dr. COLLINS. Thank you for the question. It certainly was a serious blow to momentum. The \$1.55 billion that were taken away from our budget in the middle of the fiscal year resulted in our inability to fund about 750 grants that otherwise would have been

funded that year, and those very good ideas basically got left on the table.

As you know, we were able to make up some of that ground in the subsequent years. Even in 2015, we did not recover the entire \$1.5 billion that was lost in 2013. The results of that, in terms of what they've done to investigators, who are already struggling with difficulty in getting their grants funded, really has been quite significant.

The overall likelihood, if you send your best ideas to NIH, of having that supported has dropped over the course of the last 10 years since the budgets became flat, and inflation has been eroding away at our ability to support research. It is important to point out—and you've made this point—that this is something which puts America at a limited competitiveness status as well.

If you look to see what other countries are doing—I'll show you a graph here—from 2011 to 2013 in terms of the change in percentage of GDP invested in research, you can see that countries like China and Brazil, South Korea, and so on are substantially increasing their investment—they're reading from our playbook from the 1980s and 1990s—whereas we stand alone in this graph as actually losing ground. The consequences of that is we're also losing opportunities for science, we're losing jobs, and we're potentially at risk of losing young investigators who are beginning to wonder whether there's a future for them, and some of them are starting to give up.

Senator MURRAY. The threat of that sequestration going on again in a few short months—what's that doing to you?

Dr. COLLINS. That hangs over us like a dark cloud, because if sequestration is not dealt with, we stand to lose another \$19 billion that would have gone to medical research over the coming years, and the consequences of that are really painful to consider.

Senator MURRAY. Thank you.

The CHAIRMAN. Thank you, Senator Murray.

Senator Burr and then Senator Mikulski.

STATEMENT OF SENATOR BURR

Senator BURR. Dr. Collins, Dr. Hamburg, welcome.

Dr. Collins, in your testimony, you highlighted the potential to better target medicines to specific patient needs. What role does biomarker qualification play in advancing these patient-focused therapies?

Dr. COLLINS. I appreciate the question. I mentioned that we had a 3-hour meeting yesterday between NIH and FDA, and one of our topics was biomarkers because of our shared interest in trying to move this agenda forward. As Dr. Hamburg said in her opening statement, there are lots of biomarkers that have been used for a long time. Measuring your blood pressure is basically a biomarker that we use to assess risks of cardiovascular disease and stroke.

Of course, we would love to see biomarkers developed for something like Alzheimer's disease, which she also mentioned. I pointed out this Accelerated Medicines Partnership that we're doing jointly with industry. It has that as one of its goals for Alzheimer's.

We're making sure that all clinical trials that are trying out new ideas about prevention of Alzheimer's disease use the same set of

biomarkers so that if something starts to work—maybe it’s a blood test, maybe it’s a measure of protein in the spinal fluid, maybe it’s a scan of something like amyloid or tau in the brain—we would know that, and we’d be able then to begin to utilize that for therapeutics.

Senator BURR. You’re both—NIH and FDA—participants in the Biomarkers Consortium.

Dr. COLLINS. Yes.

Senator BURR. Since the consortium was established in 2006, how many biomarkers has it qualified?

Dr. COLLINS. The Biomarkers Consortium, which is run by the Foundation for NIH, has partnership from NIH, from industry, from FDA, and from patient organizations. It is not itself charged with doing biomarker qualification. It’s charged with identifying possible biomarkers that need more research and making sure the research happens. The FDA has the role of qualifying those biomarkers if they have reached that standard.

Senator BURR. They have full determination based upon what the consortium comes up with as to whether they recognize a biomarker.

Dr. COLLINS. They need to evaluate—and I’ll certainly depend on Dr. Hamburg to specifically state the process—whether the science is strong enough for a particular biomarker to be considered validated, qualified, so that it can be used, and if rigorous studies have shown that it actually is a predictor of what you want it to predict.

Senator BURR. Dr. Hamburg, let me turn to you, if I could. FDA’s Drug Development Tool Qualification Program notes the importance of developing the animal models for use under the animal rule. A few weeks ago, your colleague, Dr. Borio, was before the committee as part of an oversight hearing.

As you know, human efficacy studies are not feasible in some medical countermeasures. Therefore, FDA’s animal rule is particularly important for such products, which is why I emphasized the importance of finalizing the animal rule guidance with Dr. Borio before this committee.

As far as I can tell, there’s been no further movement on this issue since that hearing. I’d like to ask you when is the animal rule guidance going to be finalized as required by law?

Dr. HAMBURG. Let me first begin by thanking you for all the extraordinary work you’ve done to advance public health preparedness and the development and availability of important medical countermeasures. The animal rule, as you note, is an aspect of this that is key, because we do need to develop medical countermeasures against certain threats where the disease may not exist in nature, and we would certainly never want to expose people to the disease to actually see if the new drug or vaccine actually works.

We have taken the animal rule very seriously. It’s one of those areas of regulatory science that is challenging, because we want to be able to know that by using animal data, which is often imperfect, we can make a good enough assessment of safety and effectiveness and appropriate use of a product against what is generally going to be a terrible, life threatening disease.

We have been working on the animal rule for quite a while and the best scientific strategies, engaging with the research community and, obviously, companies as well. We did put forward a draft guidance, and comment, ended on that back in August 2014. We received a lot of response, and we've had a lot of meetings—

Senator BURR. Is this a priority?

Dr. HAMBURG. It is a priority, absolutely.

Senator BURR. When are we going to have a final rule?

Dr. HAMBURG. I think it will be soon. I can't say that you'll have it before I step down at the end of the month. It has been a priority of mine from very early in my tenure. As you may know, I'd been working on many of these kinds of issues before I joined the FDA.

It is a scientific challenge, and, in fact, the draft guidance has shaped work that's being done in moving forward. It hasn't stopped progress in terms of medical countermeasure development. We will get it done, and I will go back from this hearing and remind the team that there is a very important Senator waiting for that, as are the American people.

Senator BURR. Then I would be remiss if I didn't mention at the same time, biosimilar pathways and the fact that we have yet to have that final guidance. I go to what Dr. Collins said in response to Senator Murray's statement on what happens on sequestration. You don't get the predictability. There's no consistency. You can't fund the things that you think might generate.

I would only say this, Dr. Hamburg. There are a lot of companies and a lot of efforts out there that are waiting for an animal rule to be finalized, that are waiting for a pathway for biosimilars. We just approved the first biosimilar at FDA, and we don't even have a pathway. We don't have a final guidance for the other manufacturers out there.

You have a company that had one approved, but nobody else knows how to get their biosimilars approved because there's no guidance on how to approach it. My only suggestion is that this is as important as how we fund research, and that having enough biomarkers qualified, having final guidance for biosimilars, having a final rule on the animal rule is all part of how we have a robust response to disease and we change the outcomes of patients in the future. I thank both of you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Burr.

Senator Mikulski.

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Thank you, Mr. Chairman, and thank you for both convening this hearing in the spirit in which you did, a bipartisan effort to really promote life science innovation in this country, which leads to new ideas, new research, new products that not only save lives but create jobs in our own communities.

I'm going to also welcome Dr. Collins and Dr. Hamburg here. I have the great joy of having both NIH and FDA located in my State. We have two outstanding leaders here who really, every day and every way, think about how they can advance the mission of these agencies, and I would like to thank them for what they do.

I'd like to thank them for hanging in there, because many of the impediments that are created are impediments that we create ourselves, not only to try to find new ideas, but maybe we need to get back to some old fashioned ideas of working together like the Chairman has said.

Dr. Hamburg, I know that you're leaving the FDA. I know you're going to continue to serve in many capacities. They said you're the longest serving, and I'm the longest serving, and here we are, each turning a new page.

I'd also like to take this opportunity to thank the men and women who work at both of these agencies, NIH and FDA. You have to know that for my 28 years of service and what will soon be 30 years of service, to wake up every day to think about how I can make the world a better place, and I have these two fabulous agencies where my job is to help you be you, I cannot tell you the pride and enthusiasm and joy that that has brought me.

Let me get to what I think are the three criteria for reform and then get to my questions. No. 1, let's respect the mission of the agency, and let's respect the men and women who work at the agency. Respect goes a long way to improving morale. Morale goes a long way in increasing productivity. I would hope the Congress of the United States would embrace the idea of respecting the men and women who work in our Federal agencies and not treat them as cheap throwaway lines on talk shows.

The second is adequate resources so that you can do the job and have the tools that you need. And third, let's approach reform in a targeted way, as the Chairman has indicated. Let's focus on specific problems and specific solutions.

I posit that to my members here to think about the three Rs, respect, resources, and reform that's targeted, which then goes to my question, Dr. Collins, and you, Dr. Hamburg.

Senator Murray raised the question of sequester. That then goes to predictability. Could you share with the committee the impact, because each one—like, Dr. Hamburg, in many of the reports, they say there's been a big turnover at FDA. Whether that's numerically justified, I'm not sure. So many accusations aren't justified.

Could you share with us what that means in terms of the predictability, sustainability, as well as the adequacy? We know that you need more. I tried to lift the caps and so on. What would predictability and certainty mean at FDA?

Dr. HAMBURG. Certainly, predictability and certainty is key. We hear it from the industries that we regulate in terms of how we oversee them, and it's essential to us to be able to do our job.

We need to be able to lay out programs that are not occurring in 1-year timeframes, but over time. We need to be able to recruit the best and the brightest scientists and other professionals that we can that are highly competitive outside of FDA. They need to know that they're going to be working in an environment where they're going to get the resources that they need and the support that they need in a continuing way.

We certainly need every dollar that we get. As was noted, we have a very broad span of roles and responsibilities overseeing products that matter greatly to every American every single day,

and we are stretched very thin. Uncertainty and instability in our funding programs make it harder for us—

Senator MIKULSKI. It makes it hard to recruit and retain.

Dr. HAMBURG. It makes it harder to recruit and retain and to make wise choices.

Senator MIKULSKI. Therefore, get the experience that you need. The other, then, with the predictability—what about you, Dr. Collins?

Dr. COLLINS. I appreciate the question, and, Senator, your strong support has been incredibly valuable, and we are all grieving the fact that you're planning to move away in 2 years, and we hope that this can be an opportunity for lots more conversation and effort in the meanwhile. The idea of stability is crucial for biomedical researchers, especially for those who are early in their careers. They have visionary ideas. They're fearless about taking on problems that maybe couldn't have been approached before but the technology now makes it possible.

When they are uncertain about whether there's going to be long-term support for that, it's very discouraging. Another graph I'll show you is what mostly troubles investigators today, which is what's happened to your likelihood of getting supported by NIH over the course of the last 50 years, which traditionally has run around 30 percent as your chance. It's below 20 percent now. It's running about 16 or 17 percent.

That means five chances out of six, your idea is going to get a no, and that means your science is left on the table unattended. That is enormously discouraging. If we could turn that corner—and the President's budget has—as you can see that little uptick there—aimed to try to do that—we could turn this whole circumstance around in the United States. We could regain the kind of momentum and leadership that we've had, unquestioned, over the past many decades. It is at risk if we can't do that.

Senator MIKULSKI. When is adequacy—I know my time is up, but I bring to my committee two things. During the sequester, FDA couldn't use the user fees that the private sector was paying in for them to hire. Here's the private sector giving the money after arduous work to create a contemporary PDUFA. That was one.

The very day before sequester, they announced that they had lowered cancer rates in this country 12 percent. Instead of pinning medals on people, we were getting ready to print pink slips. I think that's not the right way to govern.

The CHAIRMAN. Thank you, Senator Mikulski.

Senator Isakson and then Senator Bennet.

STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Thank you, Mr. Chairman. This is my first time publicly to be able to acknowledge the great contribution of Senator Mikulski to public health in America and her service to the American people, and I just want to thank her for all she's done. It's been a pleasure to serve with you on this committee.

Senator MIKULSKI. We're here together for 2 more years.

Senator ISAKSON. Dr. Hamburg, I don't want to be piling on, but Senator Burr is right on target, and this is a long lead-up to a

question, and I apologize for that. It's a very important question that needs to be answered.

You made a reference in your statement that some blame the lack of investment in biotechnology on the FDA, and you refuted that. It is quite true that investment follows certainty, and certainty follows regulatory processes that work. I find it troubling that the FDA has so much difficulty working through the regulatory process.

In last year's user fee bill, Congress directed you to update your regulation to fix the enforcement problems that have affected manufacturers and suppliers of medical gas. That was a year ago, yet we're still waiting on the report, and we've heard that some say there's resistance in the agency to doing so and issuing any new regulations.

Instead, the FDA seems to rely heavily and less formally on approaches such as draft guidance, which Senator Burr acknowledged, and untitled warning letters. These approaches do not offer legal certainty, regulatory certainty to stakeholders, and in the case of untitled letters, they fail to ensure any policies that are enforceable evenhandedly among stakeholders who are similarly situated.

Last May, Chairman Alexander, myself, and many members of this committee sent you a letter posing specific questions about the agency's use of draft guidance. We received the answer 10 months later, last night, 12 hours before this hearing. In that letter, you attached 172 outstanding draft guidance issues, one of which goes back to 1988.

How is this effective regulation, and how is this effective process?

Dr. HAMBURG. We are taking a very active look at the various guidances and what stage they're in. It's important to understand that a guidance is just that. It's a guidance to inform industry about our current thinking, and the process of developing a draft guidance to a final guidance is all extremely useful in that process. When the draft guidance goes forward, it enables us to put forward how we are thinking about the problem and to ask some questions and get information back to further engage with all of the critical stakeholders.

It's an ongoing process. Guidances are not regulations with the force of law, but it helps provide—especially when there is a more dynamic issue at hand, it provides a mechanism to begin an important conversation with a broader set of stakeholders and continue it to the final guidance.

I agree with you that we should not have that many guidances in draft. While the process of moving from a draft to a final guidance has value as well, having the final guidance is important and provides more certainty, as we were discussing.

It won't be me coming back before you, but I hope that soon, we will be able to demonstrate what has been done with respect to some of those guidances that are in draft that may no longer really need to be updated into final and those where we can translate it into final. This is an area where, frankly, we are not the only ones involved in shaping the guidance process, and it does have to go through a series of other reviews before it can be published as final. But I take your point.

Senator ISAKSON. One other question that relates to that point in a different way—I'm a victim of melanoma twice, and the surgeon general has issued a report that melanoma is costing America \$8.1 billion a year in health, a major portion of his most recent statements. I hear very little from the FDA regarding that.

We worked hard on the Sunscreen Innovation Act, which passed Congress last year, to try and expedite the time and extent applications for ingredients to be approved for over the counter sunscreen products. We are still waiting for that to happen. Can you tell me why the FDA is so reluctant to follow through on what Congress passed in the Sunscreen Innovation Act?

Dr. HAMBURG. We are committed to following through, and, of course, preventing melanoma is a high priority, as well as developing exciting new treatments for melanoma. But prevention comes first. We're committed to what was laid out in the Sunscreen Innovation Act in terms of responding to the identified timelines and process.

We do need to work with industry to get the data that we need to assess safety and effectiveness, and that is, of course, because these products are used widely, applied often, and, hopefully, with the right amount. They're used chronically, and we need to understand about their absorption of these chemicals and what that means for safety and efficacy in the individuals using them, including, of course, many young children who may be at greater risk in terms of chronic use.

We want to move forward. We want the American people to have more options in terms of sunscreen products and the protection that it can afford. We want to work with industry to make sure that the ingredients in those sunscreens actually work and that they're safe, especially for chronic use.

Senator ISAKSON. My time is up, but I'd like to urge you to do everything you can to expedite the implementation of those approvals. Thank you very much.

Dr. HAMBURG. Thank you.

The CHAIRMAN. Thank you, Senator Isakson.

I'm calling on Senators in order of seniority if they were here at the time of the gavel, that's what I'm doing.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman. Thank you very much for holding this hearing.

Thank you both for your leadership, and, Dr. Hamburg, I'm sorry to see you go, and I know that the Chairman feels the same as well.

A number of years ago, the Colorado bioscience community came to me and said, "We can't raise venture capital anymore in the United States. It's all going to Europe. It's all going to Asia." A lot of that had to do with the regulatory uncertainty at the FDA.

I had the opportunity in 2012, as you know, to team up with Senator Burr and Senator Hatch to write the breakthrough therapy legislation that now has created a pathway at FDA under your leadership that is responsible for the approval—a lot of people thought there were only one or two drugs in that pipeline by now.

There have been 22 drugs approved as a result of that legislation, and there are 55 more drugs in the pipeline, as I understand it.

It has succeeded beyond our wildest dreams, It's fair to say. I want to thank you for that as you begin to leave and ask you to talk a little bit about the shift in the culture at the FDA as a result of that designation and how we're going to keep that going after you leave.

Dr. HAMBURG. First, let me thank you for the work that you did on breakthrough and so many other things and for inviting me to talk to your biotech community in Colorado, and I've done it in many other places as well, including, recently, Massachusetts. Those kinds of listening sessions with the medical device and pharmaceutical and biotech industries are incredibly important, because we hear the concerns.

We heard loud and clear early in my tenure about the issues of predictability and consistency, and we looked at our programs and how we could strengthen them. The breakthrough designation has been enormously successful, as you know, more successful than we thought, and it did not come with additional resources. It's an example of something that we want to be able to continue and extend, but it does come at a cost.

The incredibly important lesson and the culture change that has come with breakthrough and have been confirmed by the success of breakthrough is the value of early engagement by the FDA with the product sponsor to really help shape the product development and research agenda, and then continuing contact. That has really made a difference. We see it in breakthrough. We see it in other areas as well as we look at some of our recent approvals.

We can see a sort of informal analysis that when we engage early, especially Pre-IND, we can really help the product development process take critical time and cost off of their product development, because we can really say, "You don't need to do that study, but do this study and use this approach," because it will get to the answers that will really make a difference in our approval process.

That's been enormously exciting. It does signal changes for the future in how FDA organizes itself and how we work with the broader research and industry community.

Senator BENNET. I hope that's right, and I've heard the same thing from developers of these drugs. They're saying that they feel that the FDA is engaging with them in a much more productive way than they used to. My hope is that we're going to hear that around medical devices and other kinds of things going forward.

I want to ask you one other question. Over the last few weeks, we've heard about infections and even deaths in California and North Carolina hospitals from CRE, a bug that CDC—I apologize for my voice today. I'm glad there are two doctors here, but you're not of any use to me that far away.

Dr. HAMBURG. But we don't always have the treatment you need.

Senator BENNET. The CDC director has called it a nightmare bacteria. Another very drug-resistant bacteria, *Acinetobacter*, has been directly affecting our wounded troops returning home from Iraq.

Senator Hatch and I, as you know, have been working on legislation to require FDA to establish a new regulatory pathway to encourage the development of antibiotics to treat serious and life threatening infections. The legislation has the support of antibiotic developers, public health groups and provider groups. Your team has been enormously helpful in working with us on the legislation.

Could you describe a little bit how this new pathway will protect patient safety while ensuring that patients who have unmet needs for antibiotics gain access to these important drugs?

Dr. HAMBURG. It's incredibly important as we face a world where antimicrobial resistance is growing that we ensure that we have new antibiotics in the pipeline, and especially new antibiotics for infections that are resistant to the available antibiotics. We see, increasingly, outbreaks in many different settings, including the duodenoscope, where antimicrobial resistance is causing a much greater and preventable burden of disease and death because we simply can't treat those infections.

The pathway that you're describing is an important one, because if you look at an infectious organism in the disease, it can be quite heterogeneous from much more minor infections to the antibiotic-resistant ones we were just talking about. If you look across that whole spectrum of patients who are infected, you have a very different risk-benefit calculation than if you focus on the more extreme, serious, life threatening cases where there's antibiotic resistance.

If we can develop a product that's targeted to that part of the spectrum, the risk-benefit calculations can come into a clearer focus. We know we need drugs, and the risks can be higher because the benefits are higher in that context. We need to make sure that physicians using these drugs understand that they're really being approved for a limited use, a special population, and should be labeled as such, and there needs to be education and awareness.

It will enable more products to be developed more rapidly and to get to patients who need them. Then we can continue to learn more about those products as they're in use and perhaps extend the indications for use. It enables us to move much more quickly off the dime to get important products to people and creates new incentives for companies to get involved because they can see a pathway that perhaps is shorter and more streamlined.

The CHAIRMAN. Thank you, Senator Bennet.

I have Senators Cassidy, Whitehouse, Collins, and Warren as the next four.

Senator Cassidy.

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. Dr. Hamburg, great job. In my 6 years here, you've made really remarkable progress. Thank you for that.

Dr. HAMBURG. Thank you.

Senator CASSIDY. You recently put out your FDA's transparency initiative. I have tried to understand your agency, but certainly don't understand it as you do. It does seem like there's different divisions that do different quality of work in terms of approving new applications. Intuitively, there are some which have higher turn-

over than others. I suspect those with lower turnover are the ones which have better output.

I see that as a diagnostic. Frankly, that indicates in those divisions with high turnover and lower output, there's probably some issue there in management, leadership, you name it, that is problematic. In your transparency initiative, will there be more information regarding that so that we in oversight can look at that on a granular level, trying to get a sense of how your successor could perhaps improve those processes?

Dr. HAMBURG. Certainly, the transparency initiative was a multifaceted undertaking intended to both expand understanding of what the FDA is, what we do, how we do it, and why, but also to hold us accountable in critical areas of activity and really post for everyone to see the progress we were making on critical issues.

You're right. The different parts of the FDA are functioning with somewhat different performance with respect to aspects of their work. It relates to both management and assuring that we have consistent, high-quality management and oversight. It has to do with having adequate resources to support—

Senator CASSIDY. Presumably, the resources somewhat flow between the two, so one division—would it have far more resources than the other?

Dr. HAMBURG. Not always, because—

Senator CASSIDY. If not always—

Dr. HAMBURG. We were talking about the user fees before—

Senator CASSIDY. I just have limited time, so let me kind of go back to my point because I have a question for Dr. Collins. If you could make that information more available, That would help us—

Dr. HAMBURG. OK.

Senator CASSIDY [continuing]. As we look on a granular level, because that is our responsibility to provide that oversight.

Dr. HAMBURG. Just one point there. The user fees are often targeted to specific programs through a negotiation process. The programs with user fees often have a bit more flexibility and, hopefully, more predictability in terms of resources.

Senator CASSIDY. I've got you.

Dr. Collins, I'm a doc, and, apparently, Senator Bennet doesn't want a gastroenterologist taking care of his cough.

[Laughter.]

Senator CASSIDY. That said, clearly, our goal is translational research, correct?

Dr. COLLINS. Yes, one of the goals.

Senator CASSIDY. Some of your grants go to MDs and some go to PhDs. Do you track what percent of those grants going to PhDs result in translational research and those which go to MDs or MD PhDs result in translational research? Is there a difference there?

Dr. COLLINS. We do track that. As you know, our workforce is made up of a variety of individuals with different backgrounds. PhDs are the majority, actually. MDs and MD PhDs are also very significant contributors. In general, the MDs and MD PhDs tend to be more focused on translation or clinical efforts, but some of them are doing basic science.

Senator CASSIDY. I get that.

Dr. COLLINS. Certainly, a lot of the PhDs are deeply engaged in translation.

Senator CASSIDY. The taxpayer wants translational research, right? I come from academics, and some people are content with writing a paper, but they're not necessarily looking forward to translation.

When you track, how much weight is given to someone's success in translation, and if someone is really successful in translation—perhaps not as good as someone else, but really successful in translation—how much would that weigh toward their future of being awarded a grant?

If you have precise statistics, I would like to know what percent of grants go to MD PhDs or MDs? What percent to PhDs? Of those going to PhDs, how many result in translational research, and of MDs, what percent? And if there is a difference, as you suggest, it does seem as if perhaps we should put weight more to the MD PhD, if their bias is toward translation.

Dr. COLLINS. I can certainly provide that data for the record.

We have, of course, encouraged translation at NIH by the founding of this new center, the National Center for Advancing Translational Sciences, which is providing resources for PhDs and MDs to enable the kind of translational science they might have trouble doing otherwise by themselves. We're very focused on this.

Just a small caveat, though. I would say we need to be careful not to discount the value of that fundamental basic science, which has been the mainstay of NIH's success over the years.

Senator CASSIDY. I totally accept that, but I do know there are some that do not take the entrepreneurial kind of next step.

Dr. COLLINS. We can help with that.

Senator CASSIDY. Last—and I'm going to say this because I've said it before—in your testimony, you mentioned the great success that we have had with HIV in terms of its eradication. I'll point out that it still seems to be 10 percent of your budget. Alzheimer's/dementia, is what, \$800 million now, and HIV is \$3 billion, which is 10 percent of the NIH budget.

CBO just released—and this won't show up well—our national debt, which they say by 2025 will be 77 percent, which they say is dangerous to our future. Knowing that we're going to go into a period of constrained resources because of our last 6 years of escalating national debt, I would again push that if HIV/AIDS, as you have mentioned, is substantially addressed—still problems, but substantially—and Alzheimer's/dementia is a balloon note, Medicare and Medicaid are just going to go bankrupt dealing with this.

We should start shifting more aggressively resources from that which has been addressed to that which we are confronting. Just making that point once more.

I yield back.

The CHAIRMAN. Thank you, Senator Cassidy.
Senator Whitehouse.

STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Thank you, Chairman.

Thank you both for being here today. Rhode Island is a small State, and we tend to have a lot of small and entrepreneurial com-

panies. I'm concerned that when there is an FDA or other regulatory disadvantage that a company must bear to bring a product online, that hits a lot harder on the small company than it does on the big one.

I notice that in the Accelerating Medicines Partnership, all the participants seem to be the big manufacturers. Obviously, if you're a big manufacturer, a world in which only big manufacturers can succeed is a good world because you don't face disruptive technologies from little manufacturers. You're probably not going to get a lot of objection from the big manufacturers.

How do you push back against the incentive of big manufacturers to squeeze out little ones and make sure that little manufacturers get the attention that they need and are included in these types of processes and are helped through your process? Since I mentioned the Accelerating Medicines Partnership, let me start with you, Dr. Collins, then I'll ask Dr. Hamburg to jump in.

Dr. COLLINS. I appreciate the question, because we are very much in support of the idea that all the partners in this ecosystem need to flourish, the public and the private. AMP actually aims to try to do that by making all the data immediately accessible to everybody, including the small biotech companies. They get to see it. This is a rather unprecedented kind of partnership.

Recognize that the pharmas that are taking part—10 companies—are paying for half of the cost of the research. This is \$230 million over 5 years, half of it from NIH grants, half of it from companies, all sitting around the same table to design the process.

It should empower everybody, what we learn through this process and making the data accessible. That would be the only way NIH could really see this as something we could support. The companies have gone along with it, which is really quite impressive on their part.

In terms of other things, we have a very vigorous small business program that supports a lot of startup biotech companies, and I could cite you a number of remarkable success stories that are now highly profitable companies that started out on the basis of an NIH grant. We are increasing, actually, our support of SBIR proposals and shortening the timetable for review of those, because often weeks matter when you're a small company just trying to get started and you need that initial infusion of grant cash to do the experiments.

We're very invested in this space. Probably one of my closest relationships in terms of working with industry is through BIO, the Biotechnology Industry Organization, going to their meetings every year, listening to their concerns, trying to be sure that we are synergistic with the whole effort they're trying to mount in terms of finding new cures, new devices, new diagnostics.

Senator WHITEHOUSE. Dr. Hamburg, my time is running down, so let me ask you to comment on that. If you could also comment on—where there's a controlled pharmaceutical, the DEA has a process that begins at the end of the FDA process that delays the ultimate approval. To my knowledge, DEA has never come to a conclusion that is different than the FDA's conclusion, which makes me wonder why we put that additional demand on the process if the outcome is inevitable.

If you could talk about those two things—the DEA process that follows yours and making sure that small providers have a shot up against the big guns.

Dr. HAMBURG. I'll try to be quick. On the small business question, it's a very serious area of focus and concern for us, because many of the medical product companies that we regulate are small on the medical device side and in the biotech world. As Dr. Collins noted, often, they are one product approval and/or a few weeks away from going under. Yet, that's where a lot of innovation occurs.

We have tried both to streamline our regulatory processes and provide more outreach and assistance through the process for small businesses to help with that process, to be more responsive and provide that additional clarity. This is one of the reasons why this investment in regulatory science is really important, because there are common tools and approaches that can be used by smaller companies that can't make the same investments, whether it's in the biomarkers area or innovative clinical trial design.

Senator WHITEHOUSE. And the DEA process?

Dr. HAMBURG. We are working on small business—high priority. DEA, it's a complicated system. It's certainly not one that we put in place. Would it be the way that we would structure the process if we were starting from scratch? We obviously make our decisions based on public health and medical care, and our perspective doesn't always align with DEA.

We do try to work closely with them in critical aspects of making important drugs available for people and in appropriate oversight of the use of scheduled drugs. I would be disingenuous if I didn't say that I have seen some of the disconnects that you have seen, and it might be an appropriate time to look at how best to align these different players in an important area of work.

Senator WHITEHOUSE. Thank you.

The CHAIRMAN. Thank you, Senator Whitehouse.
Senator Collins and Senator Warren.

STATEMENT OF SENATOR COLLINS

Senator COLLINS. Dr. Hamburg, first let me thank you for your service. You and I have discussed many times the technological breakthroughs that are making a real difference for people who are living with diabetes. An example of that is the continuous glucose monitor, which is helping patients control their blood glucose levels, which is key to preventing costly and sometimes deadly diabetes complications.

The NIH and FDA have been extremely supportive of these innovations in diabetes care, and that is why I was so surprised and troubled when CMS decided that it would not reimburse or pay for insulin-dependent Medicare beneficiaries to continue to have their continuous glucose monitors. We have a situation now where an individual with Type 1 who is covered with private insurance gets to be the age where they age into Medicare, and they lose the coverage for the CGM.

This has led me to question whether CMS consults with the FDA and NIH in making its coverage decisions. Do they consult with you, and were your two agencies consulted in the case of this denial of coverage?

Dr. HAMBURG. I have to tell you I was not aware of this situation, and I can see why it's concerning to you, and we're going to have a lot more important breakthroughs in terms of medical devices and, of course, new treatments for diabetes that will make a difference. We work with CMS. We can work more with CMS.

We've done some pilot projects with CMS to look at how we can do some of our decisionmaking in parallel rather than in series so that as data is being collected in the product development space, data that will meet the needs of both agencies can be gathered and examined. There, obviously, are discussions with CMS on various specific products. As I said, in our modern world, we need to do more of that.

I would also say that your point speaks to an issue that's been a high priority for me, and that I leave FDA feeling like we still haven't adequately addressed, which is part and parcel what you're trying to do here, which is we have to look at the whole ecosystem for biomedical product development and use and recognize that each of the different components that often operate in silos actually are very interdependent.

One of the things, for example, that I'm hearing now more and more from investors in biomedical research is that it's not the FDA regulatory process that worries them and that they see as the barrier. It's reimbursement issues and getting that right. We really need to take that ecosystem approach.

Senator COLLINS. Thank you.

Dr. Collins, I'm going to switch to a different issue just in the interest of time. I hope you'll respond for the record to my question.

Dr. COLLINS. I'll be happy to.

Senator COLLINS. You put up a fascinating chart in which you showed the tremendous progress that we've made with cardiovascular disease, with cancer deaths, and with HIV/AIDS. What they all have in common is that Congress has made a sustained investment over the years in NIH research, and it's paid dividends in better treatments and in falling death rates.

I am, as you know, very concerned about the trajectory of Alzheimer's disease, which is fast becoming our most costly disease in this country. As a society, we spend \$226 billion a year caring for people with Alzheimer's. Out of that amount, \$153 billion comes from the Medicare and Medicaid programs. As Dr. Cassidy says, the trajectory is frightening. It's going to bankrupt our healthcare system, and it's also causing such suffering for the victims and their families.

I know you mentioned the AMP and the BRAIN initiatives, and I'm excited about those. But shouldn't we be doing even more to do a concerted effort targeted at Alzheimer's, given what the trajectory of this disease is?

Dr. COLLINS. I do appreciate the question, and I share the concern. When you look at the cost of Alzheimer's disease and the care of individuals afflicted, not to mention the suffering their families go through, that individuals go through, we are on a trajectory that anybody who looks at it has to be deeply concerned about.

We are certainly ramping up Alzheimer's disease research at a pretty unprecedented rate. I just looked at the numbers. Between 2011 and the President's budget proposal for 2016, that will be a

42 percent increase for Alzheimer's disease research, greater than virtually any other area that NIH supports. Is it enough? No. Frankly, we don't have enough that I could argue to support all the ideas in lots of other areas as well.

The good news is that Alzheimer's disease research is in a very exciting place, that we do have new ideas about therapeutics. We have the ability to do drug screens on cells growing in tissue culture that represent Alzheimer's compared to normal in a way that we would not have dreamed we had that ability as a model, and these are human cells. We can start to really figure out how to address therapeutics in a systematic and rational way. There's a lot of excitement in the field about seeing that go forward.

We are doing everything we can to find those partnerships—AMP is one of them—to be sure that we're building on the capabilities of other agencies and other sources of funding. The patient advocates are a wonderful group of supporters as well.

Frankly, it is an example of the fact that we've lost about 23 percent of our purchasing power for research since 2003. We really need to be able to get back on a stable trajectory. That would benefit Alzheimer's. That would deal with this. That would deal with a lot of other things that are looming out there as our population ages.

Senator COLLINS. Thank you very much.

The CHAIRMAN. Thank you, Senator Collins.

Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman.

Thank you, Dr. Collins and Dr. Hamburg, for being here. I also want to say, as others have, thank you, Dr. Hamburg, for your many years of service. The Nation owes you a great debt.

Over the past 50 years, the American system of medical innovation has transformed the health of literally billions of people around the world. New treatments have given hope to people diagnosed with leukemia, HIV, breast cancer, and other diseases that were once a death sentence.

The basic mechanism for those remarkable achievements has two parts, a foundation of taxpayer investment in basic research followed by private industry investments that turn that research into viable products. Of the 21 drugs with the highest therapeutic impact approved between 1965 and 1992, two-thirds stem directly from discoveries made through government supported research.

A recent study in *Health Affairs* found that most of our truly transformative modern drugs have their roots in public funding. This is no accident. As we've talked about here, for decades, Congress grew the budget of the National Institutes of Health year by year. In the late 1990s, both parties worked together to double the budget for NIH.

The support has dried up. Since 2003, the NIH budget hasn't even kept up with the pace of inflation. As you note, Dr. Collins, its purchasing power is down nearly 25 percent.

Dr. Collins, can you tell us how the collapse in congressional NIH funding has hurt the American pipeline of biomedical innovation?

Dr. COLLINS. Thank you for the question, because this is the thing that worries me most and keeps me up at night. We are not taking advantage of the remarkable abilities of American science to innovate, to come up with new ideas that prevent and treat disease. One can simply look at the way in which NIH has to deal with the ideas that come to us and basically leave about half of the ideas on the table that traditionally we would have funded, and that tells you what we're doing here in terms of slowing down the process of innovation all the way from basic science through to clinical trials.

You might ask, "Well, maybe the part that we're leaving on the table is not quite as good as the stuff we're funding." We've actually looked at that, and because—when you look at that top third of applications, this is the really great science. We can't retrospectively go back and say that those that scored in the 25th percentile weren't as good as those in the 10th percentile. They're indistinguishable.

What does that say? That says we are leaving great stuff that is not getting supported and traditionally would have been. We are, of course, the foundation in many ways for this wonderful success story of American science, which is public and private working together. What we discover, as you point out, has led to those breakthroughs that now people take for granted. We can't keep taking it for granted if we don't support it.

Senator WARREN. Given how important this issue is, you'd think our first priority here would be to figure out how to get the NIH the resources it needs to replenish the pipeline of great research that is the foundation for better treatments and reliable cures. But, instead, Congress has focused on whether to lower the FDA standards for approving drugs. I hear the arguments, but this is a dangerous game.

The pain killer, Vioxx, made it through the FDA's rigorous approval process but was later found to cause heart attacks. By one estimate, it killed 38,000 Americans before being pulled from the market.

Dr. Hamburg, what impact would lowering the FDA's safety and effectiveness standards have on public health?

Dr. HAMBURG. As I said in my remarks, lowering the standards would be very, very dangerous, detrimental to the health and safety of patients, bad for the healthcare system, but also bad for our wonderful preeminence in terms of our pharmaceutical, biotech, and medical device industries in terms of their ability to actually deliver products for people who need them.

We know that FDA's standards and our requirements around safety and efficacy over the years have actually helped to shape how biomedical research, clinical research, and translational research get done—this notion of really structuring our investments in research so that we ask the right questions. We don't just publish papers, as Dr. Cassidy was saying, but we actually make sure that we're leveraging the opportunities in science and technology to get important treatments, preventive strategies, and cures to patients.

Senator WARREN. So you're saying, if I understand it, that the high standards are important, not only for public safety, but also

for help shaping the research that's going to give us the treatments that we need.

Dr. HAMBURG. Absolutely.

Senator WARREN. I want to say I am certain there are changes we could make at the FDA to help speed up the approval process and get rid of unnecessary bureaucracy. When science supports change, I am eager to make change. Lowering FDA's approval standards will not increase innovation.

We could abolish the FDA tomorrow, and we'd see tons of new products on the market. The goal isn't new products to boost profits for the industry. We don't want another Vioxx. The goal is innovative, transformative products, products that are safe and effective that will cure diseases, save money, save lives. To achieve that goal, we need to start with the NIH.

Nearly everyone in Congress says they support funding that agency. Talk is cheap, and Congress has decimated the NIH's budget, singlehandedly choking off support for projects that could lead to the next major breakthrough in Alzheimer's and many other diseases.

We could dismantle the FDA, but that won't produce new cures for the diseases that maim or kill us. If we're serious about better health for children and seniors, then Congress has to step up and make a real commitment of real dollars for scientific research.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Warren.

Senator Baldwin.

STATEMENT OF SENATOR BALDWIN

Senator BALDWIN. Thank you, Mr. Chairman and Ranking Member. I am encouraged by this bipartisan effort to examine the entire discovery and development process for medical treatments.

As someone who was raised by her grandparents—and my grandfather was an NIH-funded scientist at the University of Wisconsin Madison—you can understand that I have a long-term passion for a strong, strong Federal investment in basic research. I remain concerned that budget cuts mandated by the Budget Control Act has put medical research at risk. In fact, we've been talking about that this morning.

In fact, Dr. Collins, you have cautioned that we are putting an entire generation of scientists at risk. The average age of a researcher receiving her or his first grant is increasing, and budget cuts are discouraging young scientists from entering the field or forcing them to, in some cases, leave the country in order to continue their research.

To help address this, last Congress I introduced the Next Generation Research Act that would coordinate efforts within NIH and streamline current programs to improve opportunities for new investigators. It would also promote new policies to help increase diversity and improve the success of investigators who are applying for their second grants.

Dr. Collins, we've discussed this issue a number of times before, and I'm encouraged that you share that interest and passion here. Can you please discuss with the committee any progress that has been made through NIH's existing programs, such as the Early

Stage Investigator Program and the Director's New Innovator Award, to bolster this emerging research workforce?

Dr. COLLINS. I really appreciate the question, because this is such a fundamentally important issue if we're going to have a future where American biomedical research continues to flourish. We have, in fact, instituted a number of programs that are aimed to try to encourage that next generation to see a path for themselves as successful and visionary researchers.

One thing that we have done which has now been quite helpful in that regard, is to make sure that if you're an early stage investigator who hasn't come to NIH before with a proposal, you compete against other investigators of that sort, as opposed to being thrown into the main pool with very experienced investigators who have been at this for a while. That has done quite a bit to equalize the success rates amongst the newbies versus those who have been in this business. That is one thing.

Another thing we've done was increased the number of awards which are sort of a bridge to independence from a post-doctoral fellowship to an academic position, so-called K99R00 awards, which we are finding to be a very successful way to make that leap from a training position to an independent faculty position in a research intensive university.

We're also making sure that we have our graduate students and post-docs exposed to multiple different kinds of career paths, because not all of them need to end up as research track faculty in an intensive university. There are jobs in industry. There's jobs in policy, in journalism, many other places where PhD-level individuals are needed, and we want to be sure people find the right match for themselves.

We have started new programs, an early independence award, one that I'm quite excited about, which basically allows a very talented PhD to skip the post-doc and go directly to an independent position. I go to the presentations every year of the new awardees there, and it's the most exciting day of the year for me because of their vision and their ideas.

Similarly, we have this new innovator award, where you can't apply if you have previously had an NIH grant, and your idea has to be out of the box, groundbreaking, a little wacky in order for you to even be allowed to apply for that proposal mechanism. When we look at the output of that, it has been truly impressive, the kind of outcome we've had.

All that's great, but, of course, it doesn't solve the main problem we have, which is this loss in purchasing power for research. We can try to balance things as best we can, protect those young investigators. We can only go so far. We really need to turn the corner.

Senator BALDWIN. I appreciate that. Resources are obviously key to this as well as the coordination of programs that we've discussed in the bill that I've introduced and we'll certainly be re-introducing.

I guess the flip side of that, Dr. Collins, is what would the impact be of NIH's current programs for new researchers as well as the impressive new initiatives if Congress should not reverse sequestration?

Dr. COLLINS. We would continue to see this downward curve which is very troubling, indeed. Surveys have indicated close to 20

percent of researchers supported by NIH are now contemplating moving to another country or to another kind of career path because of the concern they have.

Last week I was in San Diego. I met with the MD, PhD training students who were in the so-called medical scientist training program. There was a room full of the most incredibly gifted, talented, future physician scientists you could imagine. In the past, when I met with groups like that 10 years ago, it was all about the science and how excited they were.

This was a group whose brows were furrowed, who are really deeply anxious about whether there's a path for them. Their questions to me weren't so much about science, but as to whether I could give them some sense of optimism about their future. I tried, but it wasn't as easy as it should have been, given the talent in that room.

Senator BALDWIN. Thank you.

The CHAIRMAN. Thank you, Senator Baldwin.

Senator Casey.

STATEMENT OF SENATOR CASEY

Senator CASEY. Thank you, Mr. Chairman. I want to thank you and the Ranking Member for having this hearing. These are deadly serious issues, the ones that Dr. Collins just spoke to about the impact of funding diminution. It's probably the worst example of pennywise and pound-foolish that we can imagine.

Sometimes it comes down to one name, one person, one case. The young girl in Pennsylvania, the 9-year-old, who, thankfully, is healthy right now—Emily Whitehead, who had a particular kind of leukemia. The only way her life was saved is because of an experimental so-called T-cell therapy that was pioneered by folks—researchers, I should say, NIH-funded researchers at Children's Hospital in Philadelphia.

I have to ask when I come to these debates about funding levels, which, frankly, are rather bizarre when you consider the positive outcomes that we have through NIH—I have to ask what if down the road, because we didn't make the investment, because Congress failed, would the next Emily Whitehead be saved? It's worth not just contemplating, but using those examples as a springboard to action.

Dr. Collins, I want to go back to something you mentioned before, and I know it's by way of reiteration, but it's important to repeat ourselves around here so people get the message a little better. Did you say that NIH has lost 23 percent of its purchasing power since 2003? Is that accurate?

Dr. COLLINS. That is, in fact, accurate. I can actually show you a graph that would maybe make that more clear. If you look there at the yellow line, that is the NIH budget adjusted for the effects of inflation. You can see the doubling that happened with that peak going up to 2003, and you can see the steady deterioration since then, and that, in fact, adds up to about a 22 or 23 percent loss in purchasing power over the last 12 years.

Senator CASEY. The other part of this, which you highlighted—and this is one I had not heard—is the percent of those contemplating moving out of the United States because of either the lack

of funding, or I guess it would be uncertainty regarding funding. What percent is that of researchers?

Dr. COLLINS. In this particular survey of NIH-funded researchers, it was 18 percent who said they were significantly contemplating that kind of drastic step.

I really appreciate you raising Emily Whitehead as an example of what we need to have more of. I met Emily Whitehead in the White House. Senator Alexander was there that morning as well. Emily was there for the announcement by the President of the Precision Medicine Initiative, as was her doctor, Carl June.

This is the kind of amazing success story that we believe is out there in greater numbers, but we have to be sure that we're investing in all of the steps that it takes to get there. I mean, what happened with Emily, you can trace back to 50 years of hard work understanding the immune system and understanding cancer, ultimately getting to that point. It didn't just arise out of nowhere.

Senator CASEY. Doctor, I wanted to ask you about the President's initiative, the Precision Medicine Initiative, in the context of Emily and other children. Tell me about how that initiative can—or any other undertaking or initiative that NIH will be involved in that will focus more on the pediatric research that leads to those breakthroughs.

Dr. COLLINS. The Precision Medicine Initiative aims to have an early focus on cancer and a longer-term effort to try to build this million strong cohort across the Nation to try to take advantage of a coalescence of really exciting technological opportunities. One is, of course, the genomic revolution, the ability to be able to get information about DNA at a remarkably low cost, considering where we have been.

Another is the advent of electronic health records, which are now the norm in many healthcare delivery systems. Another is the ability to use wearable sensors, that people are excited about having access to, to detect various aspects of human physiology, whether it's something that detects blood glucose in a diabetic, which Senator Collins was asking about, or something that is actually monitoring your environmental exposures or your diet or your blood pressure. All of those things are coming into their own.

To have a very large-scale cohort across the age distribution, across gender, across geography, across socioeconomic status, we could really begin to figure out what are the risk factors for disease and what can we do about them and how can we monitor and treat chronic disease more effectively having that large-scale effort. This is a joint effort between NIH, our partners at FDA, and the folks at ONC that are involved with electronic health records meaningful use. We're enormously excited about the way this could transform our understanding of biomedicine.

Senator CASEY. Thank you, Doctor.

Dr. HAMBURG. Mr. Chairman, can I just add one brief comment? I want to underscore that as you think about what can be done to really harness the extraordinary advances in science that are occurring today and the resources that NIH so rightfully needs and desperately needs to ensure that that important work, basic, clinical, and translational gets done, that you not forget that in order to actually see those ideas become real-world products, it has to be

accompanied by appropriate investments in FDA that give us the opportunities to develop our area of science to ford that final bridge to a real-world product and to help make sure that the investments in the research at NIH are being done in the most efficient and streamlined way as they are trying to actually move that product through the development pipeline into the product.

One of the disconnects that worries me a lot—and I’m sorry, but I have to say it since it’s my last time before this committee—is that everyone thinks that if you want to deliver on the promise of science, more investment in NIH—that is absolutely critical and foundational. You do not want an FDA that isn’t fully equipped to oversee the products that are coming before them, that isn’t well staffed to do efficient, modern regulatory reviews, and you want to be able to bring the knowledge and expertise of FDA and product development into those earlier stages of research.

Dr. COLLINS. May I say I heartily agree with my colleague and would like to endorse everything she just said.

Senator CASEY. I agree as well. Thanks, Doctor.

Dr. HAMBURG. Thank you for your indulgence.

Senator CASEY. Doctor, thanks for your service.

Dr. HAMBURG. Thank you.

The CHAIRMAN. Senator Franken.

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman, for calling this hearing, and thanks to you both for your service.

Dr. Hamburg, thank you. I worked closely with you on a couple of things, I thank you for your service, and we are sorry to see you go.

I also apologize for just getting here. I had a hearing in Judiciary that was also very important.

I’m proud to represent Minnesota, as you know, Dr. Hamburg, and our medical device industry, and we have spent some time working together. When I first got in this job Dr. Shuren came to Minnesota and had some discussions with the industry, roundtables with him, and I noticed kind of a different culture between the regulators and the device manufacturers, and I wonder why that would be.

LifeScience Alley, along with the FDA, did something—it was for the first time ever—a private-public consortium on regulatory science. I wanted to ask you how you believe that’s going. The name of it escapes me. It’s the Medical Device—

Dr. HAMBURG. Medical Device Innovation Consortium.

Senator FRANKEN [continuing]. Innovation Consortium.

Dr. HAMBURG. MDIC.

Senator FRANKEN. Yes, it says what it is. I like names like that but can’t remember them. The Medical Device Innovation Consortium—from your perspective, how has that been working?

Dr. HAMBURG. It is an example of the kind of thing we can and should be doing more of, as you note, bringing together private industry, academic researchers, not for profit organizations, and government under one organization that is committed to advancing the regulatory science needed to advance medical device development. It has grown enormously since it was started.

There was initially some skepticism perhaps, but it has grown. It has identified critical areas of research whereby advancing the research through this partnership will benefit medical device development much more broadly, because it's doing things like helping to design innovative clinical trial approaches that will make the clinical trials less cumbersome and make it easier for products to go into clinical trials to demonstrate safety and efficacy.

It is also developing computer models and other simulations where without the cost, the time, and the potential risk to patients, you can really examine whether a device is going to work and how the design should be tweaked, et cetera; looking at how we can better integrate patient-reported outcomes and their experience of using a device into the development and review process. It's focusing on some of the most important issues before us, doing it in a way that advances the science and doing it in a way that actually creates knowledge that becomes a common good for other product development in the future.

Senator FRANKEN. Thank you. We're proud that that private-public partnership is working.

I want to talk a little bit about precision medicine and what it's done. Sometimes when I think about precision medicine, I think I was born a little too early. I think of what things are going to be like 20, 30, 40, 50 years from now.

Let's talk about LDTs. The University of Minnesota has developed a panel of more than 1,200 genetic variations that can be tested to identify risks for specific genetic diseases. The Mayo Clinic, which is in Rochester, MN, has also made significant investments in developing and evaluating LDTs.

These folks are concerned that regulation that is not thoughtful or careful enough could hamper the lifesaving potential of LDTs and undermine the medical research designed to identify and target root causes of disease. I applaud the Chairman and the Ranking Member for working with the FDA and industry efforts, the whole series of briefings on this relatively new topic.

Dr. Collins, I'd like to know what role NIH will have in advising the FDA with regard to regulation of LDTs, and to what extent are your two agencies engaged with one another, which I think Senator Collins talked about—no relation. As a researcher yourself, what is your view on how the two agencies should work together to promote safe, effective technologies in a way that's ethical and safe for patients without interfering with the innovative work?

Dr. COLLINS. Senator, I appreciate the question. This is an area that NIH and FDA have been working together closely on over the years and are particularly closely working on right now to try to accomplish just what you said, to be sure that the kind of laboratory developed tests, particularly in the field of genetics, where things are growing so quickly, are offered to patients in a way that benefits them and doesn't slow down innovation, but also has appropriate oversight, particularly in high-risk situations where false results can actually lead to decisions that can be quite harmful.

FDA released back in the fall a guidance on risk-based oversight of laboratory developed tests. We think that is a very thoughtful document that has now sort of become the foundation for multiple conversations and workshops, including one just February 20th

that was held on the NIH campus, to try to get additional input about this.

What we can do, which is actually turning out to be quite a nice partnership in a very specific way, is we have already a database called ClinVar, which samples across the entire medical literature what has been reported as far as this particular DNA variation being connected with this particular disease or disease risk. That database is being curated in a way that people can find the information.

You can't necessarily look at that and know which of these should you rely upon and which might be a result that one person found but somebody else didn't. You need an expert panel on top of that—a group that we call ClinGen, which is basic clinical genomics oversight—of experts that looks at the data base and makes decisions upon the evidence about whether a particular DNA variation has been conclusively shown to be associated with a medical risk, like a BRCA1 mutation that's been seen in many people with breast and ovarian cancer, and at various levels of certainty what they think about the whole set of information that's there.

FDA is very interested in that particular NIH-funded effort in order for them to be able to have expert advice about what you can trust and what you can't. We're not the regulators. FDA has that role. This is a great opportunity for our relative roles to be nicely interdigitated, and it will be critical for precision medicine.

As we see more and more of these opportunities playing out with this cohort of a million or more people, we want to be sure that as we feed them back information about themselves that it's right and that they can trust it and it's been looked at by experts and reviewed by the regulatory agency.

The CHAIRMAN. Dr. Hamburg, since this is your last hearing in your current capacity, would you like to have the last word on that question or any other question before we wind the hearing up?

Dr. HAMBURG. On that question, I would say that the world of diagnostics is complicated. It's very, very important, because at the end of the day, it is what guides the ability of a healthcare provider or a patient consumer to make sure that they are getting the best possible treatment for the condition that they have.

Also, having accurate and reliable diagnostic tests is crucial to our actually being able to do the fundamental research that will reveal the opportunities in treatment, prevention, and care, because if the test is inaccurate, all of that research isn't going to mean much.

We think that at the core of all of this is our responsibility to make sure that diagnostic tests work, whether they're laboratory developed tests or much more advanced next generation sequencing, which Dr. Collins was talking about at the end there, which is really using genomic science and technology to give us vastly expanded sets of information so that one diagnostic tells you information about thousands, millions of potential variants, not just one diagnostic, one disease.

At the end of the day, our goal is not to create unnecessary regulation, but to be able to assure the American people, their healthcare providers, and the companies that make these products

that when a product goes into the marketplace, it will do what it says it will do. In fact, that kind of regulatory foundation is common sense.

It also is what enables innovation to be driven forward, because when you have some tests that aren't held to the same standard as other tests, then the incentive for those who are coming from the traditional device industry, developing FDA-regulated diagnostics—incentive for them to stay in that business when someone else can just create a test and market it without any of the same assessment and review is problematic.

It is kind of an interesting example of why things get very complicated, but at the end of the day, FDA's role is to help speed innovation to patients who need that innovation. We want innovation that works, innovation that will make a difference in promoting and protecting their health, and that will benefit our healthcare system and the industries that are so much a part of the U.S. economy.

Senator FRANKEN. Thank you for doing that, and I apologize, Mr. Chairman, for going so far over my time.

The CHAIRMAN. No, no. That's fine.

Senator Murray, do you have any concluding remarks?

Senator MURRAY. I would just say, Dr. Hamburg, well stated.

Thank you to both of you for excellent testimony. This was a really good hearing.

Senator Alexander, I look forward to working with you on this.

The CHAIRMAN. Thank you, Senator Murray.

Dr. Collins, just for the record, or if you know offhand, you mentioned the success rate and how it has declined over 30 years. What about the absolute number of grants? Has that gone down, too, or is that up?

Dr. COLLINS. The absolute number of grants that we fund versus those that we receive—it's been bouncing around, but it's under 10,000 now for new and competing grants.

The CHAIRMAN. Thirty years ago, it was what?

Dr. COLLINS. Thirty years ago—I'd have to get you the number for the record.

The CHAIRMAN. I was trying to compare that with the success rate.

Dr. COLLINS. Of course, the biomedical research community has grown in that time table.

The CHAIRMAN. Right.

Dr. COLLINS. I can get you the specific numbers.

The CHAIRMAN. It would be interesting to see that. Thanks to both of you.

Dr. Hamburg, thank you for being here.

Dr. HAMBURG. Thank you.

The CHAIRMAN. It's very important that you were here, and we thank you for your 6 years of service at FDA. I hope you'll accept our invitation to stay in touch with us especially over the next year as we work on these issues.

Dr. Collins, you're going to still be here.

Dr. COLLINS. I am.

The CHAIRMAN. We're going to stay in close touch with you.

This has been a good conversation, and the fact that the two of you were here helps signal the importance of it, and the attendance of the Senators. Of course, by 2017, we'll be in the midst of the user fee discussion. The issues that we intend to get into here are different from those.

What I would say to those in your agencies and to the administration is this is a train that's on a track to get to the station. It's going to get somewhere. Some of us are on the Appropriations Committee, and we'll be working on the sequestration, the funding levels. That's one thing that we can do.

There's also the question, as I mentioned, of that 42 percent administrative cost. If there are some things that we need to do, some laws we need to change, some other agencies, and if we can get that from 42 to 32, that's \$3 billion, one time. So there's the question of re-allocation.

There are questions of other obstacles that you've run into that you would say, "If you could change that, that would make our life better." This is in no way trying to diminish the accomplishments of the FDA or the NIH over the last few years. It's to say we're in this exciting era. The House, the President, the Senate are all heading in the same direction. We'd like to get there within a year or so, and we'd like to have your help in making sure we do that well.

This is an unusual opportunity to get a result in a town that doesn't that often see the President and the Republican Congress on the same train headed in the same direction toward an important station. By you being here, you helped to emphasize that, and we look forward to continuing our discussion.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time if they would like. Thank you for being here today. The committee will stand adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

RESPONSE BY FRANCIS S. COLLINS, M.D., PH.D. TO QUESTIONS OF SENATOR ALEXANDER, SENATOR COLLINS, SENATOR HATCH, SENATOR CASSIDY, SENATOR BENNET, AND SENATOR WARREN

SENATOR ALEXANDER

Question 1. We were able to move Ebola drugs into human, non-randomized trials in 3 months. What can we learn from that process and apply to other diseases that seem just as urgent and necessary as Ebola for the patients and families with those diseases?

Answer 1. Sustained, long-term investments in basic, translational, and clinical research enable NIH to build foundational knowledge for understanding biological systems and to develop potential treatments and cures for a broad range of diseases. The knowledge base and research infrastructure supported by NIH facilitates the agency's ability to respond to emerging health threats as well as scientific opportunities. If a public health emergency arises, then NIH often can leverage this knowledge base and research infrastructure, as well as longstanding collaborations with Federal and industry partners, to rapidly mobilize development of potential interventions.

For example, the rapid research response to the Ebola virus disease outbreak in Western Africa is illustrative of the importance of long-term research and infrastructure investments, effective partnerships with industry, and strong collaborations with Department of Health and Human Services agencies, especially the Food and Drug Administration (FDA) and the Biomedical Advanced Research and Development Authority (BARDA). Following the 2001 anthrax attacks, Congress significantly increased the funds appropriated for biodefense research. With these funds, the National Institute of Allergy and Infectious Diseases (NIAID) expanded investment in this area, leading to the development of medical countermeasures for bioterrorism agents as well as emerging and re-emerging pathogens. Among these investments more than a decade ago was support for NIH's Vaccine Research Center (VRC) for work on viral hemorrhagic fevers, including Ebola. Scientists at the VRC, in collaboration with industry partners, developed a vaccine against the Ebola virus that was effective in animal models of the disease and is under clinical evaluation for safety and immunogenicity in West Africa currently.

When the Ebola virus disease outbreak occurred, interest among NIAID's industry partners increased substantially, and NIAID was able to respond quickly to move candidate Ebola diagnostics, therapeutics, and vaccines that were already in development with NIH resources into clinical trials. For example, in February 2015 NIAID and its partners launched a randomized controlled clinical trial (RCT) to obtain safety and efficacy data on the investigational therapeutic ZMapp as a treatment for Ebola virus disease. ZMapp, a combination of monoclonal antibodies directed against Ebola virus developed by Mapp Biopharmaceutical, Inc., builds upon years of basic and preclinical research supported by NIAID and other partners.

The ZMapp randomized controlled clinical trial was developed in partnership with the FDA and Ebola-affected countries over a period of several months to address the urgent need of current and future Ebola patients while ensuring the trial was appropriately designed to adequately demonstrate safety and efficacy. To date, the ZMapp RCT has enrolled patients in the United States, Sierra Leone, Guinea, and Liberia. The swift progression of ZMapp and other candidate Ebola countermeasures to clinical trials was made possible because of longstanding partnerships with FDA, Centers for Disease Control and Prevention, the Office of the Assistant Secretary for Preparedness and Response (ASPR), ASPR/BARDA, and Department of Defense colleagues, as well as collaborations with industry partners and officials in the affected countries.

In response to the Ebola outbreak, NIH also was able to capitalize on its efforts in drug repurposing, which seek to identify existing drugs that could be effective treatments for diseases other than the ones they initially were developed to treat. Researchers from the National Center for Advancing Translational Sciences (NCATS) and the Icahn School of Medicine at Mount Sinai explored drug repurposing as a means to rapidly identify potential existing drugs that may block Ebola infection. The team developed a miniaturized test to screen for drugs that block the ability of Ebola virus-like particles to enter and infect cells. Miniaturizing the test enabled the team to utilize a high-throughput screening format, whereby the test could be applied to several hundred drugs at the same time. The team used the NCATS Pharmaceutical Collection, a library of 2,816 approved and investigational medicines, and identified 53 drugs with Ebola virus-like particle entry block-

ing activity. Further testing must occur before any of these drugs can be used as an Ebola treatment; however, this process highlighted how drug repurposing and high throughput screening can speed up the development of potential therapeutics to address urgent health needs.

Long-term investments in biodefense research, drug repurposing, and effective partnerships enabled NIH to respond quickly to the need for Ebola vaccines and therapeutics. Similarly, investments in other disease areas and across the biomedical research spectrum position NIH to seize opportunities or respond to needs to develop interventions that improve the health of individuals and the public.

Question 2. A former NIH director, Dr. Zerhouni commented that, “The ability of any institution to adapt to its changing environment will remain a key to its success.” How do NIH and FDA need to evolve to keep pace with where science is now? What does Congress have to do to help you get there?

Answer 2. The pace of scientific discovery moves quickly, and NIH works diligently to stay abreast of changes that could impact research needs and opportunities. First, we listen to the scientific community by sponsoring and attending workshops to understand the latest research, assess any new directions that a field may be taking, and consider whether and how NIH support could make a significant impact. In addition, most NIH grants are investigator-initiated so NIH staff are aware of the newest ideas proposed. NIH also analyzes its research portfolios using a variety of approaches, including increasingly sophisticated computational methods, to detect emerging research areas that could flourish with an influx of resources. All of these activities inform NIH’s understanding of the biomedical research landscape and influence NIH funding decisions to invest in high-quality, cutting edge research. These funding decisions are based not only on peer review of scientific merit, but also on scientific opportunities, public health needs, and maintaining a balanced portfolio of basic, translational, and clinical research.

Maintaining the agility to catalyze new scientific advances and health discoveries would be improved with long-term stability in overall NIH funding, which maximizes NIH’s ability to plan for future efforts. The President’s fiscal year 2016 Budget includes \$31.3 billion for NIH, an increase of \$1 billion over the fiscal year 2015 level. In addition, the ability for NIH to be on the cutting edge of scientific discovery is dependent upon its scientists and staff being part of the conversation, both in terms of hearing the efforts on the ground and providing a holistic view of the landscape that not all investigators are aware of. Staff serve as cross-pollinators of ideas and concepts, bridging fields and disciplines. However, current conference and travel restrictions hinder the ability of NIH staff to attend scientific meetings that enable them to participate in these discussions. We look forward to working with the HELP committee on advancing innovation.

Question 3. Do you believe that a single government agency can keep up with the rapid pace at which biotechnology is evolving?

Answer 3. Where appropriate to agency missions, a multi-agency approach is hugely beneficial to biotechnology advances and transformative to all biomedical and biotechnology research. The coordinated efforts of NIH and the Department of Energy (DOE) on the Human Genome Project (HGP) greatly contributed to the explosion of biotechnology as an industry. From that effort, we learned that the diverse perspectives of multi-agency efforts can speed up discovery by utilizing the expertise unique to each agency’s mission. For HGP, NIH provided vast knowledge on genetics and molecular biology and DOE provided insight into the effects of ionizing radiation on human biology.

The NIH Tissue Chip for Drug Screening program is an example of a current cross-agency collaboration utilizing and building upon advances in biotechnology. This program is managed by NCATS and addresses the current problem that promising medications often fail in human clinical trials because they are determined to be toxic despite promising pre-clinical studies in animal models. The research teams in the Tissue Chip program are developing alternative models for testing drug toxicity and effectiveness through the development of human-based tissues and organs on microchips. NIH intentionally invited the Defense Advanced Research Projects Agency and the Food and Drug Administration to collaborate in this program in order to aggressively meet program goals of tissue chip integration to develop a “human on a chip” that could receive regulatory approval as an alternative drug testing model.

Question 4a. Just last week it was reported that drug companies spend on average, almost 23 million hours each year complying with recordkeeping for Investigational New Drug applications. FDA and NIH have funded numerous efforts to improve the efficiency of clinical trials, such as the Clinical Trial Transformation Ini-

tiative and the Clinical and Translational Science Awards. I also received comments from a Vanderbilt researcher that emphasized the importance of increasing the efficiency with which clinical trials are conducted.

How can we better leverage these initiatives to get more drugs and devices to patients?

Answer 4a. The NCATS Clinical and Translational Science Awards (CTSA) program is actively addressing inefficiencies and roadblocks common across clinical and translational research with the long-term objective of having the CTSA sites serve as research hubs of a national network of clinical and translational science. The resources provided by these hubs are leveraged to support collaborations in education and training initiatives, share best practices and methods, promote team science, and conduct multi-site clinical studies through a shared infrastructure. By developing solutions to common problems across clinical trials and implementing them through the CTSA network, NIH can demonstrate their utility toward more efficient clinical trials and then disseminate those solutions more broadly to serve all clinical and translational research.

Recently, NCATS published funding opportunity announcements for Collaborative Innovation Awards, which are designed to stimulate team-based research across the CTSA consortium. NCATS has also announced plans to support the evolution of the CTSA program by soliciting innovative approaches to increasing clinical trial efficiency and effectiveness and by addressing the roadblocks common to clinical studies recruitment of research study participants.

Question 4b. What is the biggest hurdle to more efficient clinical trials? What are NIH and FDA doing to address this?

Answer 4b. One of the biggest hurdles to more efficient clinical trials is the current lack of standardization in the various processes required for trial initiation. NIH has ongoing efforts to address and improve clinical trial development and efficiency. In terms of joint efforts, under the auspices of the NIH–FDA Joint Leadership Council, the agencies are collaborating in a number of areas to improve efficiency and support to the clinical trial enterprise.

For example, NIH and FDA are collaborating on the development of a protocol template to guide investigators in preparing clinical trial protocols. The availability of a standard protocol template acceptable to both agencies would improve the quality of the protocol document and facilitate its preparation. It would also reduce the time needed for review and enhance the consistency of the review process. A protocol template could set a national standard for clinical trial protocol documentation and improve transparency of expectations from FDA and NIH on the quality of protocols, methods, data standards, and reporting.

NIH and FDA are also collaborating to promote the use of common data elements (CDEs) in clinical trials. A CDE is a data element defined uniformly across multiple sources or settings. Use of CDEs improves data quality and opportunities for comparison and combination of data from multiple studies and with electronic health records, and facilitates FDA's review of clinical trials. In addition to encouraging ongoing CDE initiatives, NIH and FDA are working to promote further efforts to develop, disseminate, and encourage use of general core CDEs across all clinical studies, disease-specific core CDEs modules, and disease-specific supplemental CDEs.

Also, NIH and FDA are exploring ways to enhance communication between FDA medical officers and NIH program officers who oversee clinical trial portfolios that are regulated under an investigational new drug application (IND) or investigational device exemption (IDE). Such discussions would address trial design and statistical issues that can enable the generation of sufficient evidence on the safety and efficacy of the proposed approach.

Question 5. The United States has long been a leader in biomedical innovation, but reports that our global edge is slipping are concerning. For example, China's Beijing Genomics Institute went from performing 1 percent of the Human Genome Project to analyzing 10 to 20 percent of all DNA sequenced around the world. While we hear a lot about research funding as a contributing factor, the regulatory environment here in the United States has been cited as a major contributing factor. What can we do to maintain America's global leadership in medical innovation?

Answer 5. As noted, the United States continues to be the largest public funder of biomedical research worldwide; however, a number of global indicators show that our competitive position in the life sciences is weakening. Much of this loss in position is due to a loss in purchasing power. NIH's fiscal year 2015 budget of \$30.31 billion represents a purchasing power cut of almost 20 percent compared to fiscal year 2004. Relative to the major countries in North America, Europe, and Asia, the United States now has the slowest annual growth rate in medical research invest-

ment at 1.0 percent; China (16.9 percent), Australia (9.39 percent), Japan (6.89 percent), Canada (4.59 percent), Europe (4.19 percent), and other Asian countries (20.89 percent) are all increasing their annual investments in medical research at a faster pace. Since 1992, the United States has fallen from second to tenth in overall R&D intensity (R&D investment/GDP = 2.89 percent)—now ranking behind Israel, Sweden, Finland, Japan, South Korea, Switzerland, Taiwan, Denmark, and Germany.¹ The President’s fiscal year 2016 Budget level for NIH is \$31.3 billion, an increase of \$1 billion over the fiscal year 2015 enacted level.

NIH continually seeks to refine its policies and procedures in order to speed the translation of research into health benefits. For example, NIH is currently refining its clinical research policies to promote and facilitate participant engagement in research and speed the initiation of research through the use of a single Institutional Review Board for multisite studies. At a time when increasing competition for limited funding is resulting in investigators spending more time writing grant applications and less time conducting science, NIH is looking to speed the granting process and reduce administrative burden on its investigators.

NIH is supporting a new ad hoc committee of the National Academy of Sciences National Research Council that has recently convened to examine and report on Federal Research Regulations and Reporting Requirements: A New Framework for Research Universities in the 21st Century. The committee is expected to identify regulations and reports that constitute a burden, as well as improved approaches to reduce such burdens. Its report is due in 2016. This step is in addition to ongoing activities with the Federal Demonstration Partnership and the NIH Scientific Management Review Board that also provide valuable input on ways to reduce administrative burdens.

To help maintain America’s leadership in medical innovation, NIH is also exploring strategies to further encourage the development of public-private partnerships to enhance innovation, leverage expertise and resources, and develop solutions to challenging problems. In addition, NIH is working to maximize the potential of data-sharing within the scientific community to ensure that scientific findings are accessible, transparent, and reproducible, which is key to the identification of emerging trends and breakthroughs on the horizon. Sharing data facilitates the accessibility of new research findings, prevents duplicative research efforts, and expands the range of research questions that can be addressed without generating new data. Several high-quality repositories for both clinical and non-clinical data either already exist or are under development.

Question 6. Challenges with the time and costs associated with the research, development, and approval or clearance of drugs and medical devices is not a new problem; it is an old problem that has been recognized time and time again. There seems to be a confluence of scientific knowledge, opportunity, and will to ensure that we are able to fully realize the promises that discovery have presented, and we must leverage this opportunity.

What do you see as the biggest challenges to getting safe treatments and cures to patients faster?

What do we as Congress need to do?

Answer 6. The process of turning an observation in the laboratory, clinic, and community into an intervention that can improve the health of individuals and the public—has great potential but currently is slow, expensive, and fraught with failure. By studying translation on a system-wide level, we can nurture the field of translational science to better understand the scientific and operational principles underlying the process and improve them to accelerate the process of getting treatments and cures to patients.

To address these challenges and realize the potential of scientific discoveries to improve human health substantially, the NIH established the National Center for Advancing Translational Sciences. NCATS is “disease-agnostic”; it seeks system-wide insights into what is common among diseases and the accompanying translational science process. This approach takes advantage of the increasing appreciation that seemingly disparate conditions can share underlying molecular causes, and has the potential to accelerate the development of interventions to treat more than one disease.

NCATS works with all of NIH, other Federal agencies, and many external stakeholders to identify and address common scientific and operational challenges that slow down or even block the translation of discoveries into treatments, such as finding ways to:

¹“Science and Engineering Indicators 2014” National Science Foundation, February 2014. <http://www.nsf.gov/statistics/seind14/index.cfm/chapter-4/c4h.htm#s2>.

- Better predict the safety and effectiveness of potential drugs as early as possible in the drug development pipeline;
- Conduct multi-site clinical trials more efficiently, including improving recruitment of trial participants; and
- Train a well-qualified multi-disciplinary translational science workforce.

It would be immensely helpful for the Congress to approve the President's fiscal year 2016 budget level for NIH, which proposes a \$1 billion increase over fiscal year 2015 for biomedical research, specifically including a proposal to raise funding for the Cures Acceleration Network within NCATS from \$9.8 million to \$25.8 million in fiscal year 2016.

SENATOR COLLINS

Question 1. More than 60 percent of cancers in the United States occur in people age 65 and older, and this percentage will only increase as the baby boom generation ages. As the Chairman of the Special Committee on Aging, I remain concerned that people over 65 have historically been under-represented in cancer clinical trials.

Many older cancer patients do suffer from other serious diseases and conditions accompanying the aging process, such as high blood pressure, heart disease, and dementia. While I understand that there may be concern given these comorbidities, would important lessons likely be learned about how best to treat older cancer patients if more were included in the clinical trials?

Answer 1. The relationship of cancer to age is not simple, and not all cancer types show an increased incidence with advanced age. At the same time, more than half of cancer cases are diagnosed in patients over 65 and the number of new cancer cases is expected to rise from 1.7 million today to 2.5 million by 2040. Those increases will occur almost entirely among people over 65.

Currently approximately two-thirds of patients in clinical trials are 65 or younger. Despite some increases in the numbers of patients aged 65 to 75 who now participate in trials, the number of patients over age 75 who are enrolled in trials remains low. Patients over age 75 represent 10 percent or less of clinical trials enrollment. As noted, these numbers reflect the prevalence of co-morbidities that may disqualify such patients from enrollment, as well as other factors, such as the difficulty of traveling to the sites of trials.

NCI is taking a number of steps to address these challenges, particularly through the NCI Community Oncology Research Program (NCORP) and National Clinical Trials Network (NCTN). NCORP Research Base hubs have disease-specific committees that focus on older adults. These committees have the responsibility for designing studies on treatment, cancer control, symptom management, quality of life, and cancer care delivery addressing the needs of older adult cancer patients. The NCORP network of investigators, cancer care providers, and academic institutions aims to bring cancer clinical trials and cancer care delivery research to individuals in their own communities. Research in the community setting allows access to a larger and more diverse patient population in a variety of healthcare locations. This can accelerate accrual to clinical trials, enable feasibility testing of promising new interventions, and increase the generalizability of study findings. NCORP also facilitates patient and provider access to treatment and imaging trials from NCTN.

Historically, there has also been a tendency to use less aggressive therapies in older patients with cancer. However, that approach has been changing in response to several factors. First, many have noted the importance of distinguishing between chronological age and physiological age, especially in the oldest population groups, when making treatment decisions. Older cancer patients who are otherwise in good health are now likely to receive the same surgery, radiotherapy, and/or drug therapy as relatively young patients. Moreover, it is anticipated that fewer side-effects of cancer therapy will occur as improved surgical methods are developed, radiotherapy is delivered with greater precision and better division of doses, and drug therapy shifts from traditional chemotherapy to the more targeted approaches of "precision medicine." In addition, several new immunotherapies—from the use of therapeutic antibodies to methods to strengthen the activity of immune cells—may be quite well tolerated by patients at advanced ages. To obtain the evidence regarding the use of these therapies in elderly patients, it is important that such patients are included in clinical trials. NCI continues to support the accrual of a diverse patient population.

SENATOR HATCH

Question 1. As you know, the Obama administration announced its Precision Medicine Initiative for the purpose of investing in a new generation of lifesaving discov-

eries based on the recent advances in genetic research—for many of which you are responsible by way of your leadership of the Human Genome Project and the NIH. I understand that one of the goals of the Initiative is to assemble a data base of one million volunteers. The Utah Population Data base (UPDB) is a unique resource that represents more than 7.3 million people connected to 23 million records, including vital statistics and medical records. The UPDB is the world's largest repository of genealogies, and public health and medical records, and it has been already a powerful resource for advancing precision medicine. Using the UPDB, researchers at the Utah Genome Project (UGP) have so far identified genes that contribute to more than 30 diseases.

The extensive family histories within the UPDB are made possible by a cultural emphasis within Utah on large families and carefully assembled and extensive genealogies, the combination of which aids the identification of inherited genetic mutations that cause specific diseases. The data generated by the UGP can become an international resource for genetic research. Given this brief overview of these resources, I submit to you the following questions:

Cancers are a major focus of the UGP, and it is also looking at UPDB families with exceptionally high incidences of leading chronic diseases. Multigenerational families have already been identified in which dozens of relatives are affected with the same disease, often at an unusually early age. With regard to the Precision Medicine Initiative, what are some of the specific areas that the NIH is interested in studying in effort to prevent, diagnose, and treat?

Answer 1. The National Institutes of Health (NIH) appreciates your interest in the President's Precision Medicine Initiative (PMI). The PMI at the NIH has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are now within our reach because of advances in basic research, including molecular biology, genomics, and bioinformatics.

The proposed national research cohort of one million or more volunteers will provide a robust research resource for qualified investigators to answer a wide range of questions related to the prevention, diagnosis, and treatment of disease including cancers and chronic conditions. The PMI will allow investigators to initiate research on questions that the national research cohort is uniquely poised to help answer. When the PMI is funded, the NIH Institutes and Centers will issue requests for applications (RFAs) inviting extramural investigators to propose ground-breaking precision medicine projects within the ICs' mission areas. The RFAs will be published after the Advisory Committee to the Director (ACD) has made its recommendations to the NIH Director, and the Director has made his decisions regarding implementation of the PMI at NIH in September 2015.

The PMI efforts hold tremendous promise to improve the ways we anticipate, prevent, diagnose, and treat cancers. The cancer-focused component of this initiative will be designed to address some of the obstacles that have already been encountered in "precision oncology:" unexplained drug resistance, genomic heterogeneity of tumors, insufficient means for monitoring responses and tumor recurrence, and limited knowledge about the use of drug combinations.

Question 2. UGP researchers are particularly interested in the practical application of genetic discoveries, including the discovery of potentially pivotal pathways involved in chronic diseases. Because the UPDB contains careful genealogy and phenotyping potential, the UGP has the potential to find rare disease-causing variants that could point to pivotal pathway targets—such as PCSK9 or sclerostin—for which novel medicines could be developed. Are such practical applications a goal of the Initiative? If so, what are some of the specific areas that the NIH hopes to explore? Do you see the UPDB as complementary to the mega-national cohort in potentially accelerating key discoveries?

Answer 2. It is indeed a goal of the PMI to generate the scientific evidence needed to move the concept of precision medicine into every day clinical practice. As noted above, the PMI at the NIH has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Furthermore, the initiative will tap into converging trends of increased connectivity, through social media and mobile devices, and Americans' growing desire to be active partners in medical research.

The PMI will also need to evaluate the most promising approaches to bring precision medicine strategies to a broad array of diseases in much larger numbers of people over longer periods. Toward this end, we envisage assembling over time a longitudinal cohort of 1 million or more Americans volunteered to participate in research, which may include existing health care system cohort, research cohorts, and *de novo* recruitment. On March 30, 2015, the NIH assembled a PMI Working Group of the

ACD which delivered a report to the full ACD in September that articulates a vision for building such a cohort. The resulting ACD recommendations will significantly inform what kind of resources are appropriate to include in the cohort in the near and longer term. The NIH anticipates a varied array of research activities in this new research platform that will propel our understanding of diseases—their origins and mechanisms, and opportunities for prevention and treatment—laying a firm, broad foundation for precision medicine.

Question 3. On February 11–12, 2015, the NIH held a workshop called “Precision Medicine Initiative: Building a Large U.S. Research Cohort.” Although it is the largest genetic research data base, the UPDB was not invited to participate. Do you see the leaders of the UPDB and UGP as a valuable resource that should be included in the NIH’s efforts to implement the Precision Medicine Initiative?

Answer 3. To help inform its report, the PMI ACD Working Group described above gathered inputs from a wide variety of stakeholders through a series of public workshops over several months on topics around precision medicine. One of these workshops, held on May 28–29 at Vanderbilt University, Nashville, TN, focused on recommending the optimal strategy for designing and assembling the national research cohort. Stakeholders associated with a wide variety of national resources were part of this dialog. Notably, Dr. Willard H. Dere, executive director of the Program for Personalized Health at the University of Utah, was among our panelists on our key May 28 session on leveraging existing research cohorts. In addition, a Request for Information was issued on April 20 inviting stakeholders to help guide the NIH by providing information on characteristics, purpose, or other overall aspects in the development and implementation of a large U.S. precision medicine cohort, and NIH received the input from over 150 researchers and organizations.²

SENATOR CASSIDY

Question 1. During a recent visit to NIH, Bill Gates was asked how he sets funding priorities at his foundation. He answered “Dollars for DALYS”. The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. Does NIH use a disease burden measurement, such as DALYs, to set funding priorities? If not, what do you use?

Answer 1. NIH carefully considers several disease burden measures as indicators of public health need, which is one of several key factors in priority-setting. Recent studies have shown a significant positive correlation between various measures of disease burden and NIH funding levels.^{3 4 5} However, other complex factors are important to consider when assessing public health need and the best way for NIH to fulfill its mission.

In the interests of beginning a conversation about the alignment between NIH funding levels and public health needs, NIH conducted an exploratory analysis.⁶ Though there are many potential measurements of disease burden, this analysis used both DALYs and deaths from WHO’s Global Burden of Disease 2010 study, and used both U.S. and global measurements. The plots show how NIH’s funding aligns with these four measurements of disease burden, though some measurements may be more appropriate than others for certain conditions. While this analysis has some caveats, which can be found on the site alongside the plots, NIH believes that it offers an initial picture of how NIH funding is informed by public health needs.

In addition to public health need, NIH leadership also takes into account scientific merit, scientific opportunity, and portfolio balance when deciding how to allocate resources. In short:

- **Public Health Needs:** NIH responds to public health needs, ranging from emerging infectious disease crises to the growing burden of chronic disease management, as well as rare disease research.
- **Scientific Merit:** NIH only funds research which has undergone a two-stage peer review process and which has been judged highly meritorious.

²The RFI may be accessed at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-096.html>.

³Gillum LA, et al (2011). NIH disease funding levels and burden of disease. PLOS One 6(2): e16837.

⁴Sampat BN, et al (2013). New evidence on the allocation of NIH funds across disease. The Milbank Quarterly 91(1): 163–85.

⁵Moses H, et al (2015). The anatomy of medical research: US and international comparisons. JAMA.

⁶The results of the analysis are posted at http://report.nih.gov/info_disease_burden.aspx.

- **Scientific Opportunities:** NIH constantly assesses its research portfolio in light of the latest scientific developments. Significant research advances often occur when new findings, sometimes completely unexpected, open up new experimental possibilities and pathways.

- **Portfolio Balance:** NIH strives to ensure the diversity of NIH's research portfolio. Considerations of balance must include the ratio of basic research to applied, clinical, and translational, as well as cellular to behavioral, and animal to human.

Question 2. In 2012, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) completed an evaluation of its Centers programs to determine if their methods for funding would optimally support integrated, synergistic groups of investigators, based on evolving research needs and forward-looking opportunities. Although it was a laudable effort, it appears that the evaluation relied heavily on qualitative measures, such as listening sessions, and not quantitative measures (such as the Department of Defense's use of Patents, Products, and Publications) that would be far more objective and useful. Does NIH use a standard quantitative process to review its funding decisions? Does NIH collect quantitative data on its funding decisions? And, is a comparable evaluation done on other NIH Institutes and Centers?

Answer 2. NIH conducts evaluations of its research programs using a variety of methods designed to measure the extent to which programs are operating efficiently and achieving their intended outcomes. There is value in utilizing both qualitative and quantitative approaches in these evaluations. For example, qualitative methods such as convening expert scientific panels, patient-centered focus groups, or conducting structured interviews provide data on the outcomes of a research program in regards to patient experience, scientific progress or public health impact. Quantitative measures may also provide data on outputs and outcomes that indicate scientific progress or public health impact, and can include metrics related to publications, patents, commercialization activities, and clinically relevant outcomes such as new clinical guidelines. NIH's RePORTER is a publicly available electronic tool that allows users to search a repository of NIH-funded research projects for quantitative output measures such as patents, publications, and published clinical guidelines associated with each award.

NIH evaluations often utilize a mixed methods approach and are conducted over several time points because of the long time period over which outcomes are produced. Qualitative methods such as those involving expert opinions can provide data throughout the process, but information should be collected as close as in time to the events in question to ensure recollections are accurate. On the other hand, quantifiable products culminating from research may accumulate over a period of several years, during and after the research project is completed. For example, publications are among the most immediate quantitative research outputs, and yet research data must be cleaned, analyzed, and results reported in manuscripts submitted to scientific journals. Most journals have a publication lag-time of more than 1 year from manuscript receipt to publication. Once articles are published, their full bibliometric impact on the field cannot be assessed for at least 3 years. Other quantifiable outputs such as patents will take longer, and clinical outcomes may emerge in an even longer time period as research results inform clinical care guidelines, which in turn are implemented into widespread practice.

NIH is actively working to strengthen its evaluation practices. Improvements are being made to NIH's grants administrative data bases to better track research outputs and outcomes in automated, standardized ways. Evaluations of best practices are developed and shared among staff in the Institutes and Centers through a variety of means such as regular meetings of the NIH Planning and Evaluation Officers Committee and interest groups in evaluation and portfolio analysis, including the Evaluation Special Interest Group and the Portfolio Analysis Interest Group. In addition, the Institutes and Centers often collaborate on evaluations of cross-cutting programs and trans-NIH evaluations are conducted by several programmatic offices within the Office of the Director.

Question 3. Can NIH provide an analysis of those who serve on NIH review panels by academic background: those with a degree in Medicine, those who hold science degrees, and those with both?

Answer 3. Among reviewers who served in fiscal year 2013–14, 73 percent had a Ph.D., 16 percent had an M.D., and 11 percent had both a Ph.D. and M.D. The distributions of degrees among reviewers mirror those of our applicant and grantee population, *i.e.*, 55–58 percent of investigators on R01-equivalent awards from each of these three groups have served as reviewers in fiscal year 2013 and/or fiscal year 2014. The composition of NIH peer reviewers closely resembles the composition of the grantee community in terms of race, ethnicity, and geographic location. NIH

strives to include a diverse group of well-qualified reviewers in the peer-review process, providing for the best evaluation and assessment of applications.

SENATOR BENNET

Question 1. We look forward to reviewing the work you have discussed in the President's Precision Medicine Initiative.

As you know, six of the top research institutions have joined together to form the Oncology Research Information Exchange Network, known as ORIEN. The University of Colorado is one of the participating universities.

ORIEN partners have access to one of the world's largest cancer tissue repositories and data from more than 100,000 patients who have consented to the donation of their tissue for research.

Can you talk about ORIEN's work and if the NIH plans to coordinate with ORIEN to achieve the President's Precision Medicine goals?

Answer 1. The Oncology Research Information Exchange Network (ORIEN) is entirely distinct from the NCI fiscal year 2016 Precision Medicine Initiative. In response to a request from ORIEN, NCI officials met with representatives of ORIEN in February 2015. Based on that meeting, NCI concluded that the exclusivity and commercial focus of the ORIEN structure contradict longstanding NIH and NCI data sharing principles.

Under the Precision Medicine Initiative, NCI will assemble and analyze additional genomic data sets to increase our understanding of cancer genomes and their relationship to gene variants that a patient may have inherited. Based on the genomic information we uncover, NCI will test new therapies against childhood cancers and several common adult cancers. NCI will also develop better animal and cell-based models of cancer, study mechanisms of drug resistance, and identify new therapies and therapeutic combinations to overcome drug resistance. NCI will build on what it and its research partners have already learned in ways that will accelerate the pace of discovery and deliver benefits to patients through clinical practice.

NCI's goals are to develop mechanisms for aggregating, storing, and analyzing NCI/NIH-supported data sets, genomic and clinical, in a manner that makes the information useable to all qualified researchers in a responsible manner.

Question 2. As we debate constant funding cuts in Congress, or the lack of investment in important priorities like health care and education, bioscience reform and funding continues to be one area where we have strong, bipartisan interest.

You've spoken in the past with me about how other countries approach funding in the life science area.

Can you take a few minutes to discuss with the committee how we should think about investment in life science innovation—not just as a domestic priority—but as a global economic priority to keep us competitive with other nations?

Answer 2. The United States continues to be the largest public funder of biomedical research worldwide; however, a number of global indicators show that our competitive position in the life sciences is weakening. Investment in biomedical research not only improves public health but also builds new knowledge and technology, leads to innovation in the form of new goods, services, or processes, contributes to national competitiveness, improves living standards, and furthers social welfare. The economic benefits of improved health can be staggering. Research-related gains in average life expectancy for the period from 1970 to 2000 have an economic value estimated at \$95 trillion, about \$3.2 trillion per year. For cancer alone, every 1 percent decrease in death rate has been estimated to be worth between \$440 billion and \$500 billion per year, or approximately 4 percent of the U.S. gross domestic product.⁷

While the economic benefits of investing in biomedical research are evident, NIH's fiscal year 2015 budget of \$30.31 billion represents a purchasing power cut of almost 20 percent compared to fiscal year 2004. Relative to the major countries in North America, Europe, and Asia, the United States now has the slowest annual growth rate in medical research investment from public and industry sources at 1.0 percent. China (16.9 percent), Australia (9.3 percent), Japan (6.8 percent), Canada (4.5 percent), Europe (4.1 percent), and other Asian countries (20.8 percent) are all increasing their annual investments in medical research at a faster pace. Since 1992, the United States has fallen from second to tenth in overall R&D intensity (R&D investment/GDP = 2.8 percent)—now ranking behind Israel, Sweden, Finland, Japan,

⁷ Kevin M Murphy and Robert H Topel, "The Value of Health and Longevity" U. Chicago and NBER, 2006. http://www.ucema.edu.ar/u/je49/capital_humano/Murphy_Topel_JPE.pdf.

South Korea, Switzerland, Taiwan, Denmark, and Germany.⁸ Despite Europe's current economic woes, the European Commission has urged its member nations to increase their investment in research substantially, recommending budgets of 80 billion Euros (\$95 billion) in 2014–20, a 40 percent increase over the previous 7-year period.⁹

These trends have resulted in the restructuring of the share of total global investment. As a percentage of global R&D funding, the United States declined by approximately 13 percent from 2004 to 2012, while Asian economies increased by approximately the same share. U.S. Government funding for medical research, specifically, has decreased to a 50-percent share of the world's total public research investment, down from 57 percent in 2004.¹⁰ There also have been major shifts in the composition of the global scientific workforce. From 1996 to 2011, China's science and technology workforce increased 6 percent annually to reach 1.31 million workers, now making it the largest national science and technology workforce in the world.¹¹

Policies related to life sciences R&D affect our Nation's ability to thrive in an increasingly competitive and knowledge-driven global economy. A growing number of indicators—from global R&D Investment to trends in higher education and workforce training—show that expanded investment and policies designed to enhance the life science industry have enabled several countries to become strongly competitive with the United States.

SENATOR WARREN

Question. Our health care system currently rewards private industry only for drugs that can be sold either at high cost or in very high volume. That doesn't work for antibiotics, where dosages are historically inexpensive and where new antibiotics should be used sparingly to preserve their effectiveness. Last year, HHS commissioned a report to assess the impact of different economic incentives for antibiotic development.

Based on that report and your experience, can you tell the likely impact of proposals to extend patent life for antibiotics, base approval on fewer patients, or give small increases in reimbursements for new products, on the number of new and innovative antibiotics entering the pipeline?

Policy options to stimulate antibiotic development have been considered outside of Congress, such as prize competitions, and decoupling payments from sales volume. What policy options do you think would be the most likely to increase the number of new and innovative antibiotics entering the pipeline?

Answer. The HHS report you referenced, entitled *Analytical Framework for Examining the Value of Antibacterial Products*, was commissioned by the Office of the Assistant Secretary for Planning and Evaluation (ASPE) and conducted by the Eastern Research Group. We defer to ASPE on report outcomes and impacts.

[Whereupon, at 12:04 p.m., the hearing was adjourned.]

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⁸“Science and Engineering Indicators 2014” National Science Foundation, February 2014. <http://www.nsf.gov/statistics/seind14/index.cfm/chapter-4/c4h.htm#s2>.

⁹<http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020>.

¹⁰Moses et al., “The Anatomy of Medical Research: US and International Comparisons” *Journal of the American Medical Association*, 2015. <http://jama.jamanetwork.com/article.aspx?articleid=2089358>.

¹¹*Ibid.*