

**CONTINUING AMERICA'S LEADERSHIP: THE
FUTURE OF 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 THE FUTURE OF MEDICAL INNOVATION FOR PATIENTS

APRIL 28, 2015

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CONTINUING AMERICA'S LEADERSHIP: THE FUTURE OF MEDICAL INNOVATION FOR PA- TIENTS

TUESDAY, APRIL 28, 2015

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

The committee met, pursuant to notice, at 10:03 a.m., in room SD-430, Dirksen Senate Office Building, Hon. Lamar Alexander, chairman of the committee, presiding.

Present: Senators Alexander, Burr, Isakson, Collins, Scott, Roberts, Cassidy, Murray, Casey, Bennet, and Warren.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order. This morning, we're holding a hearing on Continuing America's Leadership: The Future of Medical Innovation for Patients.

Senator Murray and I will each have an opening statement. Then we'll introduce our panel of distinguished witnesses. After our witnesses' testimony, Senators will each have 5 minutes of questions.

This is our third hearing in the committee on examining how we can get safe drugs, medical devices, and treatments from the discovery process through the regulatory process into medicine cabinets and into doctors' offices for patients who need them. Today, we have experts from the National Institutes of Health and the Food and Drug Administration who can speak to specific challenges to that process, what NIH and FDA are working on to address these challenges, and barriers that remain in their way.

Each of our witnesses today knows a great deal about innovation. Their daily work puts them up close with cutting edge technologies that are changing the face of modern medicine, from researching spinal stimulation to help paralyzed people regain control of their limbs to approving the next breakthrough medication that could cure cystic fibrosis.

In many cases, our witnesses have overseen advancements in their fields that have embraced innovation and moved the American medical field forward for patients.

Dr. Austin, for example, founded and directed the NIH Chemical Genomics Center while he was at the National Human Genome Research Institute to advance the translation of discoveries of the

Human Genome Research Project into insights on diseases and conditions and ultimately treatments.

Dr. Pettigrew established the Quantum Grants at the National Institute of Biomedical Imaging and Bioengineering to achieve medical moon shots by supporting high-risk, high-reward projects to address major healthcare problems, such as microchips to capture circulating tumor cells for early detection and to monitor treatment.

Dr. Shuren has overseen a major advancement in heart valve replacement therapy and the first approval of a next-generation gene sequencing platform. There is not much in drug innovation that Dr. Woodcock has not overseen or been involved in over the last 10 years, including the first personalized medicines.

What I hope to hear today is what FDA and NIH currently are doing and how Congress can help create the environment so the NIH and FDA keep pace with today's cutting edge scientific advancements.

Senator Burr and I released a white paper in January that looked at the process of getting drugs and devices from discovery to medicine cabinet, and much of what the report covered is relevant here today. Today, medical products take more time and money to discover, develop, and reach the American patients than ever before.

We have heard that the FDA has difficulty regulating the most cutting edge medical products. This disparity between the pace of scientific discovery and FDA's scientific knowledge is threatening America's position as a global leader in medical innovation. We read in the paper and hear stories about drugs and devices available to patients outside the United States first, such as the heart valve mentioned earlier or a drug for multiple sclerosis.

Private investment is shifting away from early stage drugs and devices in part due to increasing regulatory burden and uncertainty. Countries across the globe are seeking to capitalize on America's shrinking competitive advantage in the biomedical space.

In response to that report, we've gotten a glimpse of some of the exciting new technologies on the way. We want to make sure the FDA is ready for the developments coming, such as bioelectric medicine, where nanotechnology sends electric signals to restore nerve function; regenerative adult stem cell therapies derived and put back into the same patient; and therapies based on the whole genome sequence intended to prevent any clinical symptoms from ever occurring.

FDA has quite the task before them to keep up with these and many other technologies and to be able to judge the benefits. At our first hearing, we heard from Dr. Collins, the head of the NIH, and Dr. Hamburg, the former FDA Commissioner. Dr. Collins highlighted the need for reforms on the travel of NIH scientists and the need for the ability to roll funds over from 1 year to the next.

Dr. Hamburg said that more needs to be done on regulatory science, and that FDA needs to be involved earlier in medical product development to ensure the most efficient process.

We know that opportunities exist today: the ability to use real world data to improve health, both to shorten the time to get to market, and then also to make sure that medical products are safe

once on the market; the ability to know about a disease, including the genetic and molecular impact, and target those markers before symptoms are ever present.

Our task is to help ensure that the exciting new technologies being developed and discoveries being made are reaching patients and that the NIH is equipped to support the early stage research required to make these advancements and that the FDA is equipped to handle them.

I look forward to hearing from the panel how Congress can ensure that our biomedical research and review systems are ready for these opportunities and have the expertise and tools to address the challenges.

Senator Murray.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Well, thank you very much, Chairman Alexander. And thank you to everyone here today, especially our witnesses, for joining us.

I'm very proud to represent a State that is a leader in biomedical innovation. I see maintaining our country's central role in the life sciences as a top priority, and I believe we need to be doing everything we can to make sure the next life-saving, world-changing cures and treatments are developed right here in the United States. The conversation we're having this morning about the future of medical innovation for patients and families is a really important part of this effort.

I had the chance to visit the Fred Hutchinson Cancer Research Center in my home State of Washington recently. As I always am when I visit my State's world-class research facilities, I was struck both by how far we've come in terms of medical and technological advancement and also by how much more there is to discover.

Over the last half century, our medical system has taken huge leaps forward. We've moved from a system in which many patients had no idea whether medical products would help them, hurt them, or do nothing at all, to one in which FDA-approved treatments are the global gold standard for safety and effectiveness, a standard that patients and families have come to trust when making decisions about their health.

Clinical research has, of course, been a key contributor to this progress. I'm pleased that recently there has been increased focus on the need for clinical trials to include women, children, and other patients from all backgrounds. This is critical, because we need to understand how products work for every patient and family. I will continue to make this a priority as we look for ways to advance medical innovation.

Today, medical experts are continuing to push the limits of science and technology. We now increasingly have the capability to treat patients based on their own unique characteristics and medical histories.

In my home State alone, scientists supported by the NIH are exploring ways to stop cancerous cells from metastasizing, which is the No. 1 cause of cancer deaths, and develop 3D analysis of internal biological surfaces so devices like joint replacements can be better integrated into the human body.

These are just a couple of the many incredible examples of scientific work being done today. Our task in Congress and in our bipartisan effort to support medical innovation for patients is to support this work and ensure that our country continues to uphold the highest standards of medical safety and effectiveness.

The two questions I am especially interested in exploring today are: What more can Congress do to help get patients the best, safest treatments more quickly? In general, what role can Congress play in realizing this goal by helping to move the ball forward on the most difficult scientific challenges?

Over the last few years, Congress has put in place tools like FDA's breakthrough designation and accelerated drug approval, which have helped patients and families get treatment more quickly for serious and unmet medical needs.

One example is FDA's accelerated approval of a new drug to treat breast cancer in women. NIH estimates that in 2014, more than 230,000 women were diagnosed with breast cancer in the United States, and 40,000 died from that disease.

Until this February, there hadn't been a new drug approved for a particularly common form of breast cancer in over 15 years. FDA granted breakthrough therapy designation to help speed development of a new drug, based on preliminary evidence that the drug may offer a substantial improvement over available therapies. Then, based on a single Phase 2 study of 165 women, FDA used its accelerated approval authority to approve the drug. Now this treatment is available to patients while the sponsor completes a Phase 3 study.

This focus on regulatory flexibility, where appropriate, is helping patients and families get the care they need when they need it, and I'm hopeful we can continue to make progress on this.

Another area where I hope we can be helpful is finding ways to advance the development of new medical products for patients. We've heard from Dr. Hamburg that FDA has the fastest drug approval times in the world. But the private sector development of new medical products can take years before those products ever reach the FDA's door.

I am hopeful that as our discussions continue, we can find ways to support efforts to tackle difficult scientific challenges in the development process, and, in addition, explore innovative ways to determine which products are really going to make a real difference for patients and families, and weed out products that are not earlier on in the process.

This would reduce spending on dead ends and bring down development costs. And, much more importantly, it would help direct private sector resources to the research and development that will get the best results for patients and families.

I look forward to hearing from Dr. Woodcock and Dr. Shuren about how FDA's existing tools are working and what other steps might be helpful. I am eager to hear from Dr. Austin and Dr. Pettigrew about how our work in Congress can help break through difficult science in the development process.

I want to thank again all of our witnesses for coming and sharing your expertise with us. I'm confident that with your insight, our bipartisan effort to advance innovation for patients will be bet-

ter equipped to help tackle the medical challenges our country faces and help families and communities stay healthy.

Thank you very much, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray, and as I think the witnesses know, this innovation project is a priority of Senator Murray and me and this committee. We're working closely with the President and with the administration and with the House of Representatives, and we expect to have a result sometime during this Congress. So your participation is welcomed.

We would appreciate it if you could summarize your remarks in about 5 minutes. That way, we can have more conversation. I'm delighted to welcome you. Thank you for being here. You've got big jobs running important centers.

First, we'll hear from Dr. Austin. He is Director of the National Center for Advancing Translational Sciences, which was established in 2011. It's the newest of the 27 NIH institutes and centers. It is designed to transform translational science so new treatments and cures for disease can be delivered to patients faster.

The second witness is Dr. Roderic Pettigrew. He is Director of the National Institute of Biomedical Imaging and Bioengineering at NIH. Its mission is to improve health by leading the development and accelerating the application of biomedical technologies.

Dr. Janet Woodcock is next. She is Director of the Center for Drug Evaluation and Research at the Food and Drug Administration, which performs the essential public health task of ensuring that safe and effective drugs are available to improve the health of people in the United States. She's been there for nearly 30 years and has led many of the FDA drug initiatives.

Finally, Dr. Jeff Shuren has been the Director of the Center for Devices and Radiological Health at the FDA for over 5 years. That center is responsible for assuring the safety, effectiveness, and quality of medical devices; assuring the safety of radiation-emitting products; and fostering device innovations. Among his earlier work experience was a year detailed to Senator Kennedy's HELP Committee staff. So we welcome him back.

Why don't we begin with Dr. Austin.

**STATEMENT OF CHRISTOPHER P. AUSTIN, M.D., DIRECTOR,
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL
SCIENCES, NATIONAL INSTITUTES OF HEALTH, BETHESDA,
MD**

Dr. AUSTIN. Well, good morning, Chairman Alexander, Ranking Member Murray, and distinguished members of the committee. It's an honor to appear before you today to discuss these topics, because, as Senator Alexander just pointed out, NCATS was formed in 2011 to address the systemic issues that we're talking about today. These are issues that we deal with, and they're very important to us and we work on them every day.

It's really an honor to be here, not only to represent NCATS, but alongside my NIH colleague, Dr. Pettigrew, and our colleagues from FDA, Dr. Woodcock and Dr. Shuren, to discuss how we stimulate innovation through Federal investments in scientific research. On behalf of NCATS and the NIH, I want to thank the committee for your continued support.

I appreciate the opportunity to talk with you about some of the innovative and exciting efforts we have ongoing at NCATS to improve the process of translating fundamental understanding to interventions that will improve the health of patients. Today, I'll describe just three examples of the ways that we're doing this.

First, predicting toxicity or adverse events is one of the major reasons that drugs fail in development. This is a generic problem that bedevils every translational project, no matter what the disease is.

We're tackling this in multiple ways, one of which is through the Tissue Chip for Drug Screening program. This is a program that you may have heard about. Dr. Collins likes to talk about it. It's a collaborative effort with DARPA and with the FDA in which bio-engineered human-based organs on microchips are being developed with the intent to test drug safety and effectiveness more rapidly and effectively than current methods.

The chip that I have with me today represents a kidney, and it was actually developed at the University of Washington together with a company in Seattle called Nortis. NCATS is building on its initial phase in which there were 10 different organs, the kidney among them, developed.

We're now funding projects to link these organs together with the eventual goal within the next 4 or 5 years of having 10 organs on a chip, a human on a chip, if you will, and possibly even chips from individuals so that one could make a chip from each one of us in this room, for instance. Once completed, these integrated systems will be used as models for disease, as well as, we hope, to predict whether a drug or a vaccine or a biologic would be effective in humans and/or toxic in humans.

Another roadblock that I'm sure you've heard a lot about is that many drugs make it part of the way down the development spectrum, but then they don't progress to actual treatments. For either scientific reasons or business reasons, they're deprioritized.

To address this problem, we started a program about 3 years ago called Discovering New Therapeutic Uses for Existing Molecules. It's an innovative approach to match ideas that academic researchers have on how compounds could be used to treat currently untreatable diseases. The program matches those academic researchers with pharmaceutical industry compounds that have already undergone significant research and development and are available for testing on those other diseases.

NCATS is celebrating one of the first promising results from this program. It's a potential treatment for Alzheimer's disease. NCATS-supported researchers through this program at Yale collaborated with AstraZeneca researchers to find that an experimental compound which was originally developed by AstraZeneca as a cancer treatment could be used to treat Alzheimer's disease. The compound successfully restored brain function in mouse models of the disease, and now the Yale researchers are testing it in humans with Alzheimer's to test its effectiveness.

The third example is to address the problem of multisite clinical trials, which are the last step needed to bring most drugs to market. The current clinical trial system in the United States is extremely inefficient. The NCATS Clinical and Translational Science

Award program is addressing this problem. The CTSA sites across the country serve as research hubs to support a national network for clinical translational studies.

One example of how this program is improving the efficiency of clinical trials occurred in the aftermath of the 2013 Boston Marathon bombing, where doctors from several local hospitals in Boston quickly formed a team to design a high-quality, multisite study to examine ear injuries as a result of the blast. The CTSA hub at Harvard had an agreement in place that enabled multiple institutions to rely on a single committee to review, approve, and monitor the study. A study involving seven sites was able to get going within days instead of the typical months that this would require.

This innovative ability to streamline review of multisite clinical studies enables NIH-funded research to generate results more quickly without compromising the protection of human participants. The CTSA program is also now working on improving participant recruitment to clinical trials and to leverage electronic health records to speed clinical research.

NCATS' mission is to catalyze the generation of innovative methods and technologies that will advance the development and implementation of diagnostics and therapeutics across a wide range of diseases and conditions. NCATS looks forward to building on these recent successes, such as the ones I've just illustrated.

It's important for you to know that to accomplish this mission, because we view translation as a team sport, we collaborate on every one of our projects with other partners in government, academia, industry, patient organizations. This allows us to leverage our expertise and resources with those of our partners, thus using taxpayer dollars most effectively to bring more treatments to more patients more quickly.

Finally, a month ago, I had the privilege of hosting Senator Mikulski for a tour of our research laboratories located in Rockville, MD, which allowed me to show her some of the innovative technologies that I've just mentioned. I'd like to extend an invitation to the rest of the committee to visit and see firsthand the exciting things that NCATS is doing.

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

[The prepared statement of Dr. Austin follows:]

PREPARED STATEMENT OF CHRISTOPHER P. AUSTIN, M.D.

Good morning, Chairman Alexander, Ranking Member Murray, and distinguished members of the committee. I am Christopher P. Austin, M.D., and I am the Director of the National Center for Advancing Translational Sciences (NCATS), one of the Institutes and Centers of the National Institutes of Health (NIH).

It is an honor to appear before you today, alongside my NIH colleague Dr. Pettigrew and our colleagues from Food and Drug Administration (FDA), Dr. Woodcock and Dr. Shuren, to discuss how we stimulate innovation through Federal investments in scientific research. On behalf of the NCATS and the NIH, I want to thank the committee for your continued support and for the opportunity to talk about some of the innovative and exciting efforts that NCATS is undertaking to improve the process for transforming research discoveries into cures so that we can bring more treatments to more patients more quickly.

Recent and rapid discoveries of mechanisms of disease, sequencing of the human genome, and advances in technology have led to greater scientific opportunities that have the potential to substantially improve human health. NCATS is working on

innovative ways to improve the process for transforming these discoveries into cures so that we can bring more treatments to more patients more quickly.

NCATS defines *translation* as the process of turning observations in the laboratory and clinic into interventions that improve the health of individuals and the public—from diagnostics and therapeutics to medical procedures and behavioral changes. *Translational science* is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process. NCATS studies translation on a system-wide level. NCATS' translational science efforts focus on the entire spectrum of translational research—basic research, pre-clinical research, clinical research, medical practice, and public health. At all stages of the spectrum, NCATS develops new approaches, demonstrates their usefulness, and disseminates the findings. Patient involvement is a critical feature of all stages in translation.

INNOVATION IN METHODS AND TOOLS

The translational science approach generates new technologies and data that overcome common roadblocks to translational success, thus making the process more efficient and effective for all. One technological innovation is a bioengineered system that represents human organs, more commonly known as a tissue chip. Through the NCATS Tissue Chip for Drug Screening program, a collaborative effort with the Defense Advanced Research Projects Agency and FDA, researchers are creating human tissue chips that consist of miniature 3D models of living organs and tissues on transparent microchips. The chips contain living cells and are designed to replicate the complex biological functions of specific human organs. The tissue chips are being developed to test drug safety and effectiveness more accurately and cost-effectively than current methods. NCATS is building on its initial success in developing chips that contain single tissue or organ models by funding projects to integrate several of the organ-specific chips into a full system that represents a “human on a chip.” Once completed, these integrated systems will be used to predict whether a drug, vaccine or biologic agent would be toxic to, or effective in, humans.

NCATS shares its unique research approaches and resources so that they can be broadly applied to translational science efforts at other public and private sector organizations. In a recent collaboration with the National Institute of Neurological Disorders and Stroke, NCATS scientists incorporated an innovative approach to find a compound that could enhance the activity of the parkin protein, which is implicated in Parkinson's disease. Parkin is suspected of playing an important role in the removal of faulty mitochondria (a cell's “powerhouse”) in brain cells, but for patients with Parkinson's disease, this maintenance mechanism is disrupted. NCATS researchers designed a test (called an assay) to measure the activity of the gene for parkin. With this assay, the research team is now conducting high-throughput screens using the NCATS' chemical libraries to identify compounds that increase parkin activity. While specifically designed to address this problem, the screening and assay methods designed by NCATS researchers can be used by other scientists to solve many other translational research problems.

NCATS also applies innovative methods through its Discovering New Therapeutic Uses for Existing Molecules (“New Therapeutic Uses”) program. Launched in 2012, this initiative uses an innovative strategy that matches the ideas of academic researchers to pharmaceutical industry compounds that have already undergone significant research and development, and are available for testing on other diseases. To accelerate the “match-making” process, NCATS developed template agreements to streamline the legal and administrative process of research collaboration among multiple parties. NCATS is celebrating one of the first promising results from this program, a potential treatment for Alzheimer's disease. Alzheimer's disease is the most common form of dementia, a group of disorders that cause progressive loss of memory and other mental processes. About 5 million Americans have Alzheimer's disease, and current drug therapies can only ease symptoms of the disease without stopping its progression. New treatments—so-called disease-modifying therapies—are needed to halt Alzheimer's by targeting its underlying mechanisms. Blocking that path to therapeutic success is the costly, complex process of drug development. Through the New Therapeutic Uses program, NCATS-supported scientists at Yale University School of Medicine collaborated with AstraZeneca to find that an experimental compound originally developed by AstraZeneca as a cancer therapy potentially could be used to treat Alzheimer's disease. The compound successfully reversed brain problems in mouse models of the condition, and now the researchers are testing it in humans to assess its effectiveness. We know that there is more that we can be doing to address this disease, and multiple institutes at NIH are aggressively pursuing other research on possible clinical therapies and a better under-

standing of the changes in the brain that lead to Alzheimer's disease, including through partnerships with the private sector. To that end, the President's fiscal year 2016 Budget includes \$638 million for Alzheimer's disease research.

COLLABORATION AND PATIENT ENGAGEMENT

NCATS also applies innovative approaches to translation by fostering collaboration and patient engagement. NCATS' Rare Disease Clinical Research Network is a highly collaborative network of 22 clinical research consortia and a data management center. The network is composed of approximately 2,600 researchers, including NIH scientific program staff, academic investigators, and members of 98 patient-advocacy groups. Scientists from multiple disciplines at hundreds of clinical sites around the world work together with patient advocacy groups to study more than 200 rare diseases. Since its launch, nearly 29,000 patients have been enrolled in network clinical studies. Ninety-one studies are currently under way.

The NCATS Therapeutics for Rare and Neglected Diseases program establishes robust collaborations among NIH, academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies to support faster translation of drug discovery and development. When successful, these projects are acquired by biopharmaceutical companies for further development toward approved treatments for patients.

A NATIONAL NETWORK FOR CLINICAL AND TRANSLATIONAL RESEARCH

The NCATS Clinical and Translational Science Awards (CTSA) program focuses its efforts on addressing the inefficiencies and roadblocks in clinical and translational research, from scientific discovery to improved patient care. The 62 CTSA sites serve as research hubs to support a national network for clinical and translational studies. The hubs 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. A good example of such collaboration happened in the wake of the April 2013 Boston Marathon bombing. Doctors from several local hospitals quickly formed a team to design a high-quality multi-site study to examine blast-related ear injuries. Harvard's CTSA hub had an Institutional Review Board reliance agreement in place that enabled these institutions to rely on a single committee to review, approve, and monitor the study. Therefore, this seven-site study was launched within weeks rather than the more typical months. This innovative ability to streamline the review of multi-site clinical research studies enables NIH-funded research to generate results more quickly without compromising the protection of human participants. NCATS has announced plans to support the evolution of the CTSA program by soliciting innovative approaches to increasing clinical trial efficiency and effectiveness, addressing the roadblocks common to clinical studies recruitment of research study participants, and supporting collaborative innovative research in both translational science and its methods.

CONCLUSION

NCATS' mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. NCATS looks forward to building on its recent successes to bring more treatments to more patients more quickly.

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

The CHAIRMAN. Thanks, Dr. Austin.
Dr. Pettigrew.

STATEMENT OF RODERIC I. PETTIGREW, Ph.D., M.D., DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD

Dr. PETTIGREW. Good morning, Chairman Alexander, Ranking Member Murray, and distinguished members of the committee. It is an honor to appear before you today along with my distinguished colleagues on this panel, Doctors Austin, Woodcock, and Shuren, to discuss some of the tremendously exciting innovations made pos-

sible by Federal investments in biomedical research with a focus on medical impact.

I want to thank the members of this committee for your continued support, for holding this hearing today, and for the opportunity to share our work with you. The National Institute of Biomedical Imaging and Bioengineering, commonly known as NIBIB, conducts research that sits at the intersection of the physical sciences, the life sciences, and engineering. Together, these disciplines are creating new biomedical technologies to improve health.

We serve as a catalyst for emerging technologies and a stimulator of innovation across the NIH in academia and industry. I think it is worth noting that our working definition of innovation is simply invention put to use. In laboratories that we fund across the country, innovative research is working on developing breakthrough technologies.

I'd like to show and tell you about a few of these in a brief video. These examples provide a broad view of NIBIB-supported technologies at various stages of development from proof of concept to commercialization.

[Video Shown.]

This video entitled "Eight Awesome Technologies Your Tax Dollars are Paying to Create" provides this overview. The first one is a tissue engineered human liver. It looks like a contact lens. It can be implanted in a mouse. It grows in a mouse and turns the mouse's metabolism into a human-like function. It then allows one to evaluate candidate drugs for toxicity and biological features.

This is a hand-held MR assistant which is capable of detecting a variety of targets from bacteria to viruses to components of cancer cells. This is quite an innovation that provides a completely portable, hand-held, take it anywhere you can go, fully functional ultrasound system that replaces the conventional system that you saw there. It would cost about 1/20th of a conventional system, and I have one here in my left hand that I'm holding up. This was a partnership with General Electric.

This addresses the devastating problem of paralysis due to spinal cord injuries. Implantation of the electrical stimulator at the lumbar spine in an epidural type of stimulation allows the patients that were treated who were completely immobilized for several years to regain voluntary motion as you saw in the video.

This addresses the problem with the availability of organs to transplant in patients, extending the time of presentation from 1 day to 4 days in order to identify a greater population of patients that might benefit from such transplantable organs.

This addresses a problem with vaccination and makes it a simple process that is painless with a vaccine that can be delivered in the mail. It uses this biodegradable patch that you see here that's the size of a thumb. I actually have one of those here. You place it on the skin, press it, and you're vaccinated. It is biodegradable and dissolves in about 5 minutes so you don't have the hazardous waste to be concerned about, and it's a stable temperature so you can send it in the mail.

This is an optical needle microscope that is battery powered. You place it on the surface. It provides sufficient magnification that you can identify healthy cells, distinguish those from cancerous or pre-

cancerous cells, as being shown here, and therefore provides a point of care test for identifying cervical cancer and oral cancer, as was done in this clinic in Botswana.

This final example addresses a problem of visualization of tumors at the cellular level. This innovation developed by a Nobel laureate has a molecule that seeks out cancer cells and fluoresces after it enters the cells. You can see the tumor there that was fluorescent. Similarly, for nerves, those are demonstrated as well so that the surgeon can be better able to distinguish nerves from cancer cells and potential entwining of the two.

Those are examples that illustrate the type of innovative technologies that we are developing. In summary, our institute, NIBIB, drives innovation. We innovate technologies that expand medical knowledge. We innovate diagnostics and therapies for this and future generations. We integrate engineering with the physical and life sciences to catalyze practical solutions to complex biomedical problems.

Our goal is to accelerate the creation of usable technologies to improve human health across the Nation and worldwide. I thank you for the opportunity to appear before you today, and I look forward to your questions.

[The prepared statement of Dr. Pettigrew follows:]

PREPARED STATEMENT OF RODERIC I. PETTIGREW, PH.D., M.D.

Mr. Chairman and members of the committee: I am pleased to present this testimony to you for the hearing on Biomedical Innovation. I am Roderic I. Pettigrew, Ph.D., M.D., Director, National Institute of Biomedical Imaging and Bioengineering (NIBIB). We are 1 of 27 Institutes and Centers at the National Institutes of Health. NIBIB is a relatively new IC. It was created in December 2000 and we awarded our first grants in 2002. NIBIB supports more than 800 grants and the work of more than 5,000 researchers, and an Intramural Research Program at NIH. At NIBIB we focus on creating biomedical technologies to improve health.

Our mission is to lead the development and accelerate the application of biomedical technologies to improve health. We are advancing medical care through better understanding, prevention, detection, and treatment of disease. We conduct and support emerging technology research and development that lead to innovative biomedical solutions. Integrating engineering and physical sciences with life sciences by building partnerships with industry, academia, and other Federal agencies is a high priority for the institute. In this testimony I share a few examples from the many exciting NIBIB-funded research efforts, which are leading to practical innovations that advance public health.

REVERSING PARALYSIS THROUGH SPINAL STIMULATION TECHNOLOGIES

Spinal cord injury can be devastating and affect almost anyone, from victims of auto accidents, to athletes, to soldiers on the battlefield. An estimated 276,000 people were living with a spinal cord injury in 2014. Each year approximately 12,500 new cases occur.¹

Once thought of as an injury with no hope of recovery, a novel therapy that involves electrical stimulation of the spinal cord has restored function to an unprecedented degree in 7 patients treated to date. This is a first-of-its-kind experimental study funded by NIBIB. Following treatment, severely paralyzed patients recovered everyday bodily functions, including bowel, bladder and sexual function. The return of these important basic functions has dramatically improved the quality of life of all who were treated. These patients also regained the ability to voluntarily stand and achieve limited limb movement, providing hope that further recovery may be possible with improvements to this treatment approach. Although this research is still in its infancy and not yet at the clinical trial stage, it has given real hope to people living with paralysis around the world. They have seen the positive impact

¹*Spinal Cord Injury Facts and Figures at a Glance*. February 2015. The National SCI Statistical Center, The University of Alabama at Birmingham.

in the small group of study participants and are eager to have such technologic advances transform their lives as well.

NEXT GENERATION CELL ENGINEERING

Our immune systems are highly proficient at attacking and destroying anything viewed as foreign when it enters the body. Yet cancer cells are largely ignored by the immune system because they are derived from our own cells and retain some of the same characteristics. A relatively new approach tested through a grant funded by NIBIB, uses cell engineering to reprogram the immune system to identify cancer cells and destroy them. In a recent advance, researchers have developed a vaccine made of nanoscale biomaterials that is injected under the skin. Once injected, the nanomaterials form a 3D scaffold, creating a relatively large surface area for the immune system to assemble “killer” cells specifically programmed to attack tumors. The power of this approach was demonstrated in a mouse model, in which the 3D vaccine generated a potent immune response to lymphoma cells and inhibited tumor growth. While this study tested the feasibility of a single cancer vaccine, the same scaffold could also hold different antigens or drugs to treat a range of cancers or infectious diseases. This research promises a new class of therapeutic agents which harness and enhance the power of our natural defense mechanisms against disease.

ADVANCING PRECISION MEDICINE: EARLY DETECTION OF CANCER CELLS AT THE POINT-OF-CARE

Many therapies today work well for some people, but not for others. Matching a treatment to the unique features of an individual’s disease is the goal of the President’s Precision Medicine Initiative. NIBIB is supporting research in technology development to realize the vision of customized treatment. For example, researchers have developed a miniature palm-sized device to isolate rare circulating tumor cells from a small routine blood sample. Tested in a proof-of-concept study, this novel device was able to isolate breast cancer cells from the blood of 36 women. Physicians were then able to grow the tumor cells from six of the blood samples in the laboratory to characterize their genetic and molecular features and test sensitivities to drugs. A subset of these human cells were able to also grow tumors in mice where the effectiveness of the selected drugs in inhibiting tumor growth was demonstrated. In this initial study, treatments were not given to patients; however this approach successfully demonstrated the potential to identify a range of genetic changes, or mutations, in an individual’s cancer cells to enable personalized therapy.

MOBILE TECHNOLOGY TO ADVANCE HEALTHCARE

Depending on a variety of factors, such as environmental exposure and lifestyle, individuals with the same genetic makeup can have very different health outcomes. The use of mobile technology has the potential to greatly assist researchers in gaining a better understanding of the environmental and behavioral factors that cause disease with the goal of preventing or intervening in the process. Today, smartphones are natural points of engagement for the large percentage of U.S. adults who own them. Interfacing smartphones with a variety of biosensors may allow the linkage of an individual’s electronic medical records and genomic data with information captured by the smartphone on environmental exposure and behavior if it were done with appropriate security and privacy protections. From measuring secondary smoke exposure to counting steps, or testing vision, smartphones can record, track, and transmit a significant amount of health information. Smartphones can also be used as a tool for healthier living. They can be programmed to send automatic reminders to take a medication or an alert when a dose is missed. The overarching potential application relevant to the Precision Medicine Initiative is to link and enrich the genomics and electronic health record data with a broad range of medical exposure and lifestyle information. This set of “big data” can then be evaluated or “mined” to identify new ways to improve human health.

BRAIN INITIATIVE

Approximately 100 billion neurons and 100 trillion connections make up the human brain and there is an enormous amount to explore and discover in this, the most complex of all human organs. As an institute that is very active in the BRAIN Initiative, which has been a priority for the President, as outlined in his fiscal year 2016 Budget proposal for an additional \$70 million, NIBIB supports research that leads to the next generation of neuroscience discovery tools and technologies. These technologies are being developed to advance our understanding of the function of

neural circuits and systems in health and disease. In one example, researchers are developing a completely new noninvasive method for portable 3D human brain visualization called Magnetic Particle Imaging. Based on intrinsic bioelectric properties and the use of injectable magnetic nanoparticles, this project could provide higher imaging clarity and a completely new way to characterize and understand changes in brain circuit function in mental and neurological disease.

CONCLUSION

NIBIB drives technological innovation to expand biomedical knowledge and create improved diagnostics and therapeutics for this and future generations. By integrating engineering with the physical and life sciences, NIBIB develops practical solutions to complex biomedical problems. These advances are improving human health across our Nation and worldwide.

The CHAIRMAN. Thank you, Dr. Pettigrew.
Dr. Woodcock.

STATEMENT OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. WOODCOCK. Thank you, Mr. Chairman. I'm really pleased to be here to discuss the State of medical product development, an activity that is so critical to human health, including, in our case, at CDER, combating emerging infections like Ebola, finding treatments for rare diseases, enabling healthy aging, and preventing the development of disease at all.

CDER, the Center for Drug Evaluation and Research that I lead, has a big impact on drug development, both domestic and worldwide. I'm pleased to report, as reflected in my written testimony, that a large number of innovative new medicines are being approved and are in the pipeline. In fact, U.S. patients do, in the vast majority of cases, have first access to these treatments.

To ensure continued safety monitoring of these drugs after approval, we've developed the cutting edge Sentinel network that can analyze information from 178 million Americans' medical records without compromising their privacy and watch over these new medicines after they're approved.

Congress has had a big role in these successes, from activating the PDUFA program that provides adequate resources for FDA to monitoring development of drugs and provide advice to developers as well as review the applications in a timely manner. Congress also directed establishment of Sentinel for safety and in FDASIA started the breakthrough designation program that has been highly successful in getting the most innovative drugs to patients quickly.

There are still problems, as already has been mentioned. Drug development costs too much and takes too long. This is mainly caused by the high failure rate. Even for the drugs that make it to human testing, 8 out of 10 of those fail in human testing. It's not due to the FDA requirements, but because they don't work or because they're too toxic or they're no better than existing drugs. The problem is really with failure rate.

FDA published the Critical Path Report that I actually authored in 2004 to bring attention to these problems and start working on solutions. There are many steps that have been taken. There are many steps that can be taken. For example, Chris Austin described what NCATS is doing, which is a focused effort on trying to improve the situation. But we do need to continue to improve the effi-

ciency of drug development if we're going to continue to get drugs to patients rapidly and affordably.

Now, in particular, I thank Senators Hatch and Bennet for their leadership introducing the PATH Act to establish a limited population antibacterial drug program which could be helpful in addressing unmet needs in a very fragile area of antimicrobial drug development. I look forward to working with the committee as this provision advances. I also look forward to working on other aspects of the overall challenges of drug development.

Now, one caveat, as you consider options, is, as we say in medicine, first do no harm. When CDER receives a large number of unfunded mandates, our attention can be diverted and review performance suffers. This happened after the FDA Amendment Act in 2007, and I have a chart that we will provide you that shows the dip in FDA performance following enactment of that statute.

As we consider actions to enable innovation, we need to make sure that we don't break what is working but that we improve on the current system.

Thank you, and I look forward to your questions.

[The prepared statement of Dr. Woodcock follows:]

PREPARED STATEMENT OF JANET WOODCOCK, M.D.

Mr. Chairman and members of the committee, I am Dr. Janet Woodcock, Director of the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). I am privileged to have the responsibility to oversee much of FDA's efforts to review the safety and efficacy of new pharmaceuticals. Thank you for having me here today to give you my views on current efforts and areas for improvement.

When I came to FDA in the 1980s, the process by which FDA approved new drugs for marketing to patients was under considerable criticism—for being slow, for lagging behind other countries, and for lacking transparency to, and collaboration with, the developers of new drugs.

Today, thanks to the efforts of those across the Agency, our Nation's drug review process reveals a very different picture—we are delivering new, lifesaving therapies to patients faster than any other developed country and more expeditiously than ever before. In 2014, almost two-thirds of the novel ("new molecular entity") drugs approved by CDER (26 of 41, 63 percent) were approved in the United States before receiving approval in any other country. In addition, we have significantly strengthened the drug safety surveillance system in the United States, modernized drug review processes, and introduced new genomic and related sciences into the drug evaluation process.

First Approved in the U.S.



Almost two-thirds of the novel drugs approved by CDER in 2014 (26 of 41, 63%) were approved in the United States before receiving approval in any other country.

FACTORS SPEEDING DRUG REVIEW AND DEVELOPMENT

No single action or programmatic change has brought us to where we are today; rather, it has been a steady program of improvements, new investments through PDUFA, new authorities and other factors. These improvements were based upon both externally and internally identified gaps, so that now we have more predictable review times, additional FDA resources to adequately address the workload from applications, and additional interaction between FDA staff and drug manufacturers to ensure promising drugs reach patients quickly.

PRESCRIPTION DRUG USER FEE PROGRAM

The approval by this committee of the Prescription Drug User Fee Act of 1992 (PDUFA) has been one of the most important components of our improvements in review times. As its name suggests, PDUFA provided funds in the form of user fees for FDA to hire sufficient staff to undertake the growing workload of applications to market new drugs in the United States. But it had much broader implications. It established the principle that timely review was important, not just to manufacturers, but also to patients, and that FDA should commit to conducting those reviews in a predictable manner.

I became Director of CDER not long after PDUFA's enactment and was determined from the start to ensure that the program was run in a business-like fashion, with use of modern project management techniques, establishment of specific goals, and accountability on the part of review staff and managers to adhere to those goals. The result has been a concerted effort across the Center with steady lowering of review times, greater predictability for industry, and most importantly, faster patient access to new therapies.

So, I thank the committee for the user fee program. It has helped revolutionize our Nation's drug review process speeding access to new drugs and without compromising the Agency's high standards for product safety, efficacy, and quality. In 2014, CDER met its PDUFA goal dates for 98 percent of the novel drugs we approved (40 of 41).

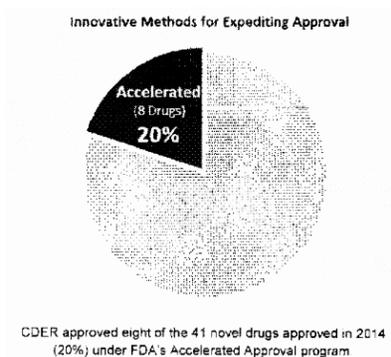
In addition to PDUFA, there have been a number of other important initiatives that have contributed to our progress in achieving these goals, including expedited FDA review programs, greater collaboration with industry, and the use of surrogate endpoints to advance drug development.

EXPEDITED FDA REVIEW PROGRAMS

FDA's expedited review programs were established in recognition of the need to find ways for therapies intended for serious conditions in patients with unmet medical needs to get into the hands of patients and health professionals more quickly.

Accelerated Approval

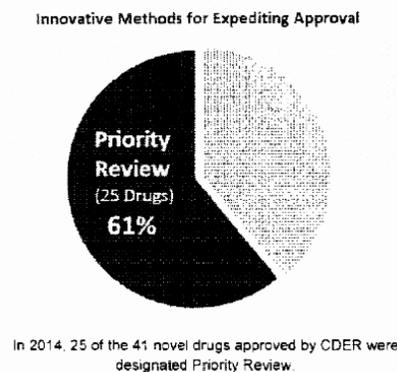
Around the time of PDUFA's passage, FDA created an "Accelerated Approval" program to permit certain drugs intended to treat serious and life-threatening medical conditions to be approved on the basis of a "surrogate endpoint"—that is, using a biomarker or measure that is "reasonably likely" to predict clinical benefit instead of directly measuring benefits to patients. As a condition of accelerated approval, sponsors must conduct or complete required post-approval studies to confirm that the drug actually helps people. Surrogate endpoints serve as stand-ins for clinical endpoints that measure the real benefits of drugs: whether a patient actually feels better or can function better, or lives longer. Surrogate endpoints generally allow clinical studies to be conducted in smaller populations of individuals over shorter periods of time, reducing both the time and cost of drug development. More information about how surrogate endpoints and other biomarkers are being used to advance drug development is included below.



CDER has approved over 90 new drug and biologics applications more rapidly because of the Accelerated Approval program. In 2014, CDER approved 8 of the 41 novel drugs approved (20 percent) under FDA's Accelerated Approval program.

Priority Review

Drugs with the potential to deliver a significant improvement in safety or effectiveness over existing therapy for serious or life-threatening illnesses may also be designated for "priority review." Priority review drugs receive a shortened, 6-month FDA review goal. For example, from the beginning of 2008 through the end of 2014, 93 novel drugs and biologics approved by CDER received the shortened, 6-month review dictated by priority-review designation. In 2014, 25 of the 41 novel drugs approved by CDER were designated Priority Review.



Fast Track

Another expedited program that helps reduce the time to market for drugs being developed for serious and life-threatening illnesses is known as "fast track." Fast-Track designation generally may be used for drugs intended to treat a serious condition where nonclinical or clinical data demonstrate the drug's potential to address an unmet medical need.

When a drug receives Fast-Track designation, FDA works closely with its sponsor to facilitate submission of the drug development plan, the design of clinical trials, and to identify any other data necessary to support FDA approval of the drug. Moreover, once the sponsor begins to develop the data to support approval, it can submit that data for "rolling review." Rolling review allows a sponsor to submit portions of a marketing application in advance of the entire application, rather than submitting all portions of the marketing application at once, which is the usual process.

Seventy-six novel drugs and biologics were approved by CDER from 2008 to 2014 with Fast-Track designation. Seventeen of the 41 novel drugs (41 percent) approved by CDER in 2014 were designated as Fast Track.

Innovative Methods for Expediting Approval



Seventeen of the 41 novel drugs (41%) approved by CDER in 2014 were designated as Fast Track.

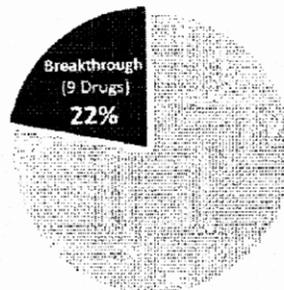
Breakthrough Therapy Designation

In 2012, Congress provided the “Breakthrough Therapy” designation as another new tool for expediting important new advances in therapy for serious and life-threatening illnesses.

Breakthrough therapy designation may be granted for a drug that is intended to treat a serious condition, where preliminary clinical evidence (i.e., in people) indicates that the drug may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies. Such breakthrough therapies, like drugs that receive Fast-Track designation, receive intensive guidance from FDA, to help sponsors better tailor their drug development program and, thus, maximize the prospects for a rapid and successful path to approval. In addition, breakthrough therapy drugs receive an organizational commitment from FDA’s senior managers and experienced review staff to collaborate in advancing the review of these potentially high-impact drugs.

As of April 16, 2015, CDER and the Center for Biologics Evaluation and Research (CBER) have designated more than 84 new therapies as breakthrough therapies, and 24 have received marketing approval. Moreover, initial experience with the breakthrough process has yielded more rapid FDA review times in many cases and shortened overall development times for these therapies. Continued success of the breakthrough therapy drug program is expected as a result of FDA’s intensive collaboration with new drug sponsors. CDER designated 9 of the 41 novel drugs (22 percent) approved by the Center in 2014 as breakthrough therapies.

Innovative Methods for Expediting Approval



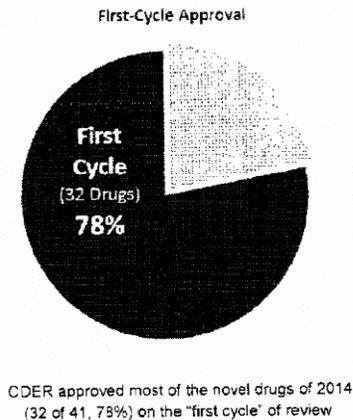
CDER designated nine of the novel drugs (22%) approved by the Center in 2014 as breakthrough therapies.

GREATER COLLABORATION WITH INDUSTRY

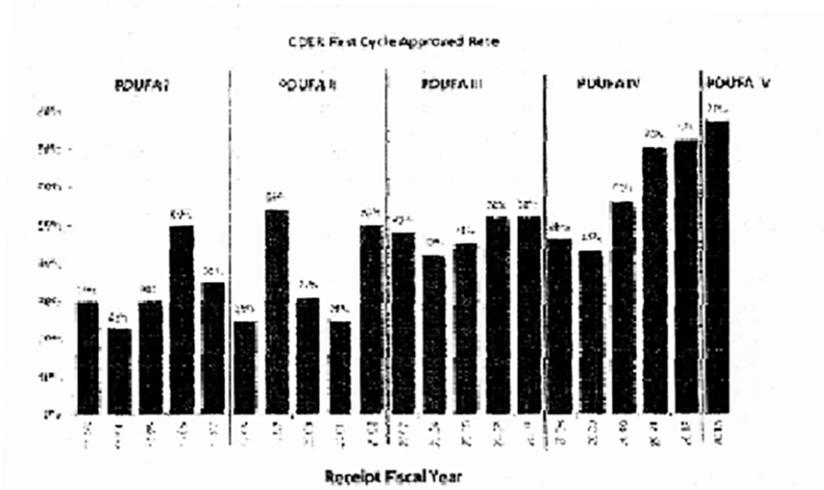
The movement toward greater collaboration between industry and FDA, embodied in such initiatives as the Breakthrough Therapy program, is reflected throughout our efforts and is one of the more significant changes that has occurred during my time at FDA. In recent years, meetings between FDA and industry have become routine and have proven to be invaluable in improving communication about planned clinical trials, development milestones, and data requirements.

The impact of improved FDA/industry communication is becoming increasingly evident. Recently, FDA took a look at the development times of new drugs that were approved with the benefit of pre-Investigational New Drug (IND) meetings and compared them to the development times for drugs that were approved without such meetings. The results were quite remarkable. For instance, for all new drugs approved between 2010 and 2012, the average clinical development time was more than 3 years faster when a pre-IND meeting was held, than it was for drugs approved without a pre-IND meeting. A 2014 article in *The Lancet*, “Biomedical research: increasing value, reducing waste” (January 11, 2014), noted that 85 percent, or \$200 billion, of annual global spending on research is wasted on badly designed studies, and I believe that greater industry-FDA collaboration can significantly reduce such wasted effort.

Another result of improved collaboration between industry and FDA is a substantial reduction in the number of application review “cycles.” The phenomenon of “multiple review cycles” occurs when a sponsor submits a marketing application for approval and FDA does not approve the drug during the first-review cycle. The most efficient outcome for both the Agency and industry is for an application to receive approval on the first-review cycle, if the drug is ultimately approvable. Not receiving FDA approval on the first cycle means that the sponsor must go back and take steps to collect additional data or address a deficiency in their marketing application and then resubmit their application, which FDA must then review again. But achieving first-cycle approval requires a well-prepared application with no major deficiencies.



As a result of better collaboration between industry and FDA, which has helped companies identify the data and analyses needed for approval before the application is submitted, first-cycle approvals, which until recently occurred for fewer than half of all novel drug submissions, are now exceeding 70 percent. For example, CDER approved 78 percent of the 41 novel drugs it approved in 2014 on the first cycle. This translates into reduced costs for industry and earlier patient access to new therapies, as illustrated by the charts. The early and frequent communications that characterize some of the expedited development programs were not possible before user fees were established, so, once again, I commend this committee for the authorization—and reauthorization—of the user fee program.

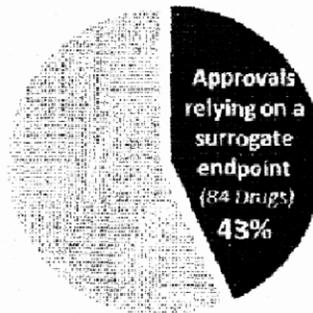


USING SURROGATE ENDPOINTS TO ADVANCE DRUG DEVELOPMENT

As noted above, FDA routinely permits the use of surrogate endpoints as the basis for Accelerated Approvals, when the surrogate is reasonably likely to predict clinical benefit in a serious or life-threatening disease that lacks good therapies. However, when scientific study has progressed sufficiently to establish the correlation between the surrogate endpoint and clinical benefit, the surrogate endpoint then may be relied upon as the basis for traditional approval, thereby negating the need for the confirmatory studies requirement, to which drug sponsors are subject, under Accelerated Approval. For example, reducing elevated blood pressure levels is a well-known surrogate endpoint to reflect reduction in cardiovascular outcomes such as stroke. Over many years, FDA has allowed the traditional approval pathway to be used in approving a wide range of blood pressure medicines, thereby dramatically expanding options for fighting stroke and other related cardiovascular conditions.

During the last 5 years (2010–14), out of a total of 197 novel drugs and original biologics approved across FDA, 84 (43 percent) relied upon a surrogate endpoint for approval. A table listing the surrogate endpoints relied upon for these 84 approval determinations (covering both traditional approvals and accelerated approvals) is attached as an appendix.

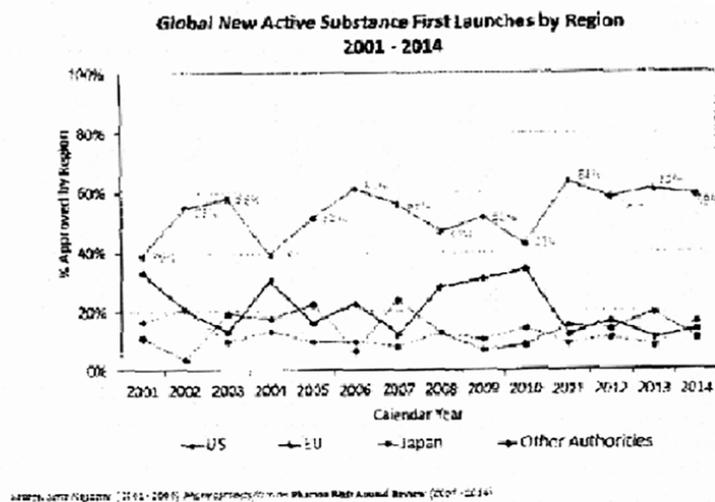
Novel drugs approved relying on a surrogate endpoint (2010-2014)
 197 total novel drugs/biologics approved; 84 relied on surrogate endpoint



A GROWING RECORD OF ACTION ON NEW THERAPIES

Each of the improvements noted above has contributed to speed both the development and the review of new therapies to prevent and fight disease. This past year provides an example of how those improvements are working; FDA approved 51 novel drugs and original biologics, 41 by CDER, 10 by CBER. Additionally, 21 of these 51 novel drugs were for orphan diseases.

The lag in approval times compared to approvals in other countries that existed many years ago has been reversed. Today, FDA approves drugs faster on average than all other developed nations: 40 days faster than Japan; 70 days faster than Canada; and 174 days faster than the European Union (EU). As the British-based Centre for Innovation in Regulatory Science recently reported, over 75 percent of the new drugs approved by Japan, EU, Canada, Australia, Switzerland, and FDA, from 2004 to 2013, were approved first by FDA. Yet, another independent analysis concludes that FDA continues to lead the EU and other advanced regulatory authorities in the introduction of novel drugs, as shown by the following graph.



The most important effect of this progress is that American patients with untreatable or poorly treated diseases are receiving the newest therapies rapidly and well before their counterparts in other nations. In addition, the major enhancements that FDA has made in the drug safety surveillance system means that American patients can also be confident that these newly approved drugs continue to have intense scrutiny after they are marketed in the United States to detect any unexpected side effects and allow for quick and appropriate FDA action.

THE PATH FORWARD

Despite the progress that has been made, and as this committee has noted, there are hurdles to overcome, if we are to ensure continued U.S. leadership in the biomedical sciences. While Congress and FDA have worked successfully together to greatly reduce FDA review times, many of the serious challenges for drug development occur before FDA review even begins. If the explosion in basic scientific knowledge is going to efficiently translate into the treatments and cures patients need, we must work together to overcome critical infrastructure and scientific hurdles that prevent the advances we all desire. In January 2015, the Administration unveiled the Precision Medicine Initiative, a vital new research effort to catalyze improvements in targeting treatment to the right patient at the right time. Launched with a \$215 million investment in the President's 2016 Budget, the Precision Medicine Initiative promises to arm clinicians with new tools, knowledge, and therapies that will work best for each patient. Below, I have described a few specific areas which advance the development of new therapies for patients.

Reducing Clinical Trial Costs

First, the cost of clinical trials continues to grow and is the greatest source of cost increases in medical product development. Today, developers of a new medicine spend many millions of dollars planning a clinical trial, developing an elaborate trial infrastructure, finding and enlisting investigators, conducting the trials, and managing the trial data. Each time a new drug is tested, the process is repeated, at great expense, only to dismantle the infrastructure when the study is completed.

We believe that there are ways to greatly improve clinical trial efficiency, such as widespread use of clinical trial networks and master protocols, and we would like to work with you to examine those possibilities.

Enhancing the Science of Biomarkers and Other Tools

Second, the science of identifying and evaluating the utility of biomarkers and other scientific tools must be greatly enhanced. These tools can be used to predict and evaluate the effects of candidate drugs, both before clinical testing, and in people. Biomarkers are technically defined as physical, biochemical, or genetic characteristics that are objectively measured and evaluated as indicators of health, disease, or in assessing the response to a therapeutic intervention. In other words, biomarkers are the results of tests done on the body, such as blood sugars or a chest x-ray. Biomarkers have many uses in drug development, such as identifying appropriate patients to enroll in a clinical trial, performing safety monitoring, and selecting therapy for treating specific patients. Hundreds of biomarkers are used today in drug development. However, biomarkers based on new scientific understanding have been slow to come into clinical use, largely because the evidence supporting their validity has been lacking. The lack of new, well-understood biomarkers also impacts drug development, these new tests could speed evaluation of drug performance, including drug safety, and prediction of effectiveness. Similar to the problems with clinical trials, the scientific infrastructure for evaluating the validity of new biomarkers has not kept pace with the need for this activity.

Typically, drug sponsors interact with FDA about new biomarkers during clinical drug development, when an IND has been filed for a new molecule. These discussions are confidential, and while new biomarkers may be used in a specific drug development program, they are not necessarily subject to broad scientific scrutiny. To address this situation, CDER recently established a Biomarkers Qualification Program. In this program, biomarkers that have demonstrated performance for a certain use are designated by FDA as *qualified biomarkers*, and can be used during the regulatory process by any developer for that specific context of use. These qualified biomarkers are only a subset of the biomarkers FDA has used in the review process.

FDA recognizes that there is still confusion about how new biomarkers can be qualified through this process. Some believe that many biomarkers are “stalled” in the qualification process. The actual case is that most of the programs in the biomarker qualification process are still in the evidence-gathering stage—which may take considerable time due to the need for more development work within the scientific community.

However, it is important to note that biomarkers do not need to go through this formal qualification process, and most do not. As mentioned previously, FDA has the ability to work directly with drug sponsors who wish to utilize various new biomarkers within their drug development program. For example, sponsors can propose a surrogate endpoint—one type of biomarker—to be used in clinical trials based upon the scientific communities’ existing knowledge about the particular surrogate endpoint. A sponsor can request FDA’s agreement on this surrogate endpoint through the “Special Protocol Assessment” process that is embodied in the PDUFA program. These product-specific surrogate endpoints are one example of biomarkers that do not need to pass through our formal qualification process in order to be used to support drug development and review. Biomarkers are also important in the growing field of so-called “personalized” or “precision” medicine, in which drugs are targeted at a genetically determined or other disease characteristic that only occurs in a subset of people with the disease. Targeted drug development is one of the most promising areas for future drug therapy. Patients are chosen for treatment based on specific test results (such as a genetic test or other biomarker), indicating that the patient’s disease (tumor, hepatitis C, cystic fibrosis) is likely to respond to the drug.

In the early 1990s, targeted therapies represented only 5 percent of FDA’s new drug approvals. In recent years, roughly one-quarter of the drug approvals has been supported by targeted drug development programs, and that rate appears to be growing over time. Important, new, recently approved, targeted cancer treatments include: Mekinst (trametinib) and Tafinlar (dabrafenib) for forms of melanoma; Imbruvica for forms of lymphoma and leukemia; and Zykadia (ceritinib) for a form

of lung cancer. The development of such targeted therapies is clearly expanding rapidly. Similarly, targeted treatments for other diseases have been approved, including treatments for cystic fibrosis and ground-breaking treatments for hepatitis C that are potentially curative for the majority of treated patients. As targeted therapies become ubiquitous, advances in standardizing and increasing our understanding of the biomarkers that enable use of these therapies will be necessary.

Harnessing Evidence from Clinical Experience

Another source of information about drug effects is evidence from clinical experience (called “real world evidence” or “big data,” by some). I have aggressively developed FDA’s Sentinel Initiative, a national electronic system that is transforming FDA’s ability to track the safety of drugs and biologics once they reach the market. Sentinel enables FDA to actively query diverse health care data sources—such as electronic health record systems, administrative and insurance claims data bases, and registries—to evaluate possible medical product safety issues quickly and securely. The Sentinel Initiative is one of the largest uses of this type of information in health care and is proving vital for monitoring safety and analyzing safety signals. But the science of using evidence from clinical experience to establish product effectiveness, e.g., to evaluate new uses of drugs, is still in its infancy. So we must first develop the methodologies needed to harness its promise.

Strengthening Patient Engagement

The final example focuses on making patient experience more central to drug development. FDA recognizes that patients living with a chronic disease are experts in the effects of that disease and its current treatments. As you know, the FDA Safety and Innovation Act (FDASIA) instructed the Agency to begin a process for incorporating more patient experience into drug development, and we have had numerous public meetings to gain important insights from patients. But we recognize that information needs to be collected in a structured and representative way to be most useful in drug development. I hope that we can work with you to further the movement toward patient-focused drug development in your upcoming legislation.

CONCLUSION

There are other areas in which we hope to work with you as well, including modernizing drug manufacturing, encouraging the development of new antibiotics, and improving the processes for FDA review of drug/device combination products. I believe all of the challenges I have described above are ones on which FDA, the drug industry, and patient groups have common interests. We look forward to working with Congress to address these challenges in ways that will serve patients and pharmaceutical innovation well.

Thank you again for inviting me to share my views today.

Attachment

NOVEL DRUGS—APPROVED USING SURROGATE ENDPOINTS*

(January 1, 2010–December 31, 2014)

Before the U.S. Food and Drug Administration (FDA) approves a drug or biologic, the product must show substantial evidence of effectiveness in clinical trials and that the benefits outweigh the risks. Clinical trials measure benefit using clinical endpoints, surrogate endpoints, or other types of measurements. Clinical endpoints measure how a patient feels or functions better, or lives longer. Surrogate endpoints are biomarkers, such as a laboratory test, radiographic image (e.g., x-rays, MRIs), and physical sign (e.g., blood pressure), that substitute for clinical endpoints in certain circumstances.

A surrogate endpoint may serve as the basis for traditional approval when it is known, through scientific study, to predict clinical benefit. A surrogate endpoint may serve as a basis for Accelerated Approval when it is reasonably likely to predict a drug’s intended clinical benefit. Drugs approved under Accelerated Approval are subject to the requirement of post-approval confirmatory trials.

From 2010–14, FDA approved 197 novel drugs, known as new molecular entities (NMEs), and New Biologic Approvals that include both New Drug Applications (NDAs) and Biologic License Applications (BLAs). The following table shows the 84 NME drugs and original biologics approved during that time period that relied upon

*In the last 5 years, FDA approved 197 novel drugs and biologics; 84 relied upon surrogate endpoints.

a surrogate endpoint for an approval determination (i.e., traditional approval or Accelerated Approval). Many of these drugs have orphan designation, which means that they are intended to treat rare or uncommon diseases.

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
1/25/2010	Victoza (liraglutide)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (H _g A1C)
2/19/2010	Morveo	prevention of meningococcal A, C, Y, and W-135 infection	✓			Immunogenicity
2/24/2010	Prenar13	prevention of invasive pneumococcal infection	✓			Immunogenicity
2/26/2010	Vpsiv (viralglucuronase alfa)	Type 1 Gaucher Disease	✓		✓	Hemoglobin (Hgb)
3/18/2010	Carbaglu (carglumic acid)	urea cycle disorder, N-acetylglutamate synthetase (NAGS) deficiency	✓		✓	Ammonia, glutamine, citrulline levels
5/24/2010	Lumizyme (alglucosidase alfa)	non-infantile onset Pompe disease (8 years and older)	✓		✓	Forced Vital Capacity (FVC) ***
6/1/2010	Prolia (denosumab)	osteoporosis	✓			vertebral fractures on xray
7/10/2010	Alpha-1-Proteinase Inhibitor (human)	treatment of alpha-1-proteinase inhibitor deficiency	✓		✓	Protein levels
9/14/2010	Krystrinx (pegloticase)	gout	✓		✓	plasma uric acid level
11/13/2010	Egrifta (tesamorelin for injection)	Lipodystrophy in human immunodeficiency virus (HIV) patients	✓			percent change in visceral fat by computerized tomography (CT) scan
2/17/2011	Factor XIII Concentrate (human)	prophylactic treatment of factor XIII deficiency		✓	✓	Pharmacokinetics
2/25/2011	Edurno (azilsartan medoxomil)	hypertension	✓			Blood pressure (BP)
2/28/2011	Dakresp (roflumilast)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1) ***
3/16/2011	Adenovirus Vaccine, Live, Oral Type 4 and Type 7	prevention of infection with two adenovirus types	✓			Immunogenicity (for Type 7)
4/6/2011	Caprelsa (vandetanib)	Medullary thyroid cancer	✓		✓	Progression Free Survival (PFS)
5/2/2011	Trajenta (linagliptin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (H _g A1C)
5/13/2011	Victrelis (boceprevir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
5/20/2011	Edurant (rilpivirine)	human immunodeficiency virus (HIV)	✓			viral load
5/23/2011	Incivek (telaprevir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
6/15/2011	Nulojix (belatacept)	organ rejection prophylaxis	✓		✓	biopsy proven acute rejection (BPAR)
7/1/2011	Arcapta Noohaler (indacaterol maleate)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
8/19/2011	Adcetris (brentuximab vedotin)	1) Hodgkin's Lymphoma; 2) Systemic anaplastic large cell lymphoma		✓	✓	1) Overall objective response rate (ORR) using computerized tomography (CT) or positron emission tomography (PET) scans; 2) overall response rate (ORR)
8/26/2011	Xalkori (crizotinib)	non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (ALK) positive mutation		✓	✓	Objective response rate (ORR) using computerized tomography (CT) or magnetic resonance imaging (MRI)
10/14/2011	Ferriprox (deferasirox)	Transferron iron overload due to thalassemia		✓	✓	serum ferritin
11/16/2011	Jakafi (ruxokinib)	myelofibrosis	✓		✓	Percent reduction in spleen volume by computerized tomography (CT) or magnetic resonance imaging (MRI)
11/18/2011	Erwinaze (asparaginase erwinia chrysanthemi)	acute lymphoblastic leukemia (ALL)	✓		✓	trough asparaginase activity level
1/17/2012	Voraxaze (glucarpidase)	methotrexate (MTX) toxicity	✓		✓	plasma methotrexate (MTX) levels
1/27/2012	lytix (axitinib)	renal cell carcinoma (RCC)	✓			Progression Free Survival (PFS)
1/20/2012	Erivedge (vismodegib)	basal cell carcinoma	✓			Objective response rate (ORR)
1/31/2012	Kalydeco (ivacaftor)	cystic fibrosis, G551D mutation	✓		✓	Forced expiratory volume in 1 second (FEV1)
2/10/2012	Zoptan (tafluprost)	glaucoma	✓			intraocular pressure (IOP)
3/27/2012	Omontys (peginesatide)	anemia in chronic kidney disease	✓			Hemoglobin (Hgb)
5/1/2012	Eliysio (taliglucuronase alfa)	Type 1 Gaucher Disease	✓		✓	spleen volume by magnetic resonance imaging (MRI)

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
6/8/2012	Perjeta (pertuzumab)	HER-2 positive metastatic breast cancer	✓			Progression Free Survival (PFS)
6/14/2012	MenBrix	prevention of meningococcal A and C and haemophilus influenzae B infection	✓			immunogenicity
7/20/2012	Kyprolis (Carfilzomib)	multiple myeloma		✓	✓	Overall response rate (ORR) by International Myeloma Working Group (IMWG) criteria
7/23/2012	Tudorza Pressair (acridinium bromide)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
8/27/2012	Stribid (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)	human immunodeficiency virus (HIV)	✓			viral load
8/29/2012	to-figastin	chemotherapy-induced neutropenia	✓			absolute neutrophil count (ANC)
9/4/2012	Bosulf (bosutinib)	chronic myelogenous leukemia (CML)	✓		✓	Major Cytogenetic Response (MCR)
10/17/2012	Jetrea (criptastemin)	vitreomacular adhesion (VMA)	✓			Vitreomacular adhesion (VMA) by central reading
10/26/2012	Synbo (omacetaxine mesoprecitate)	chronic myelogenous leukemia (CML)		✓	✓	Major Hematologic Response (MHR)
11/29/2012	Cometiq (Cabozantinib)	Medullary thyroid cancer	✓		✓	Progression Free Survival (PFS)
12/14/2012	Idusig (ponatinib)	chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)		✓	✓	Major Cytogenetic Response (MCR) and Major Hematologic Response (MHR)
12/14/2012	Signifor (pasireotide diacetate)	Cushing's disease	✓		✓	urine free cortisol level
12/21/2012	Jantapid (bimatopide)	homozygous familial hypercholesterolemia (hFH)	✓		✓	Serum low density lipoprotein-cholesterol (LDL-C)
12/28/2012	Sirturo (bedaquiline)	Multidrug resistant (MDR) pulmonary tuberculosis (TB)		✓	✓	time to sputum culture conversion

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
1/25/2013	1) Nesina (alogliptin), 2) Osetna (alogliptin pioglitazone), 3) Kazano (alogliptin/metformin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HbA1C)
1/29/2013	Kynrevo (impromsen)	homozygous familial hypercholesterolemia (hFH)	✓		✓	serum low-density lipoprotein-cholesterol (LDL-C)
2/8/2013	Pemalyst (pomalidomide)	multiple myeloma		✓	✓	Overall response rate (ORR) by European Group for Blood and Bone Marrow Transplant (EGBMT) criteria
2/22/2013	Kadcyla (ado-trastuzumab emtansine)	HER-2 positive metastatic breast cancer	✓			Progression Free Survival (PFS) using computerized tomography (CT) or magnetic resonance imaging (MRI) ***
2/26/2013	Ospheo (ospemifene)	dyspareunia and/or vaginal dryness due to vulvar and vaginal atrophy	✓			parabasal and superficial cell maturation index on vaginal smear and vaginal pH***
3/29/2013	Inovikana (canagliflozin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HbA1C)
5/10/2013	Breo Ellipta (fluticasone furoate and vilanterol trifluoroacetate)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
5/29/2013	Mekinist (trametinib)	unresectable or metastatic melanoma with BRAF V600E or V600K mutations	✓		✓	Progression Free Survival (PFS)
5/29/2013	Tafinlar (dabrafenib)	unresectable or metastatic melanoma with BRAF V600E or V600K mutations	✓		✓	Progression Free Survival (PFS)
7/12/2013	Gilexif (afatinib)	NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations	✓		✓	Progression Free Survival (PFS)
8/12/2013	Tivicay (doxigegravir)	human immunodeficiency virus (HIV)	✓			viral load

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
10/3/2013	Divavee (conjugated estrogens/bazedoxifene)	osteoporosis	✓			Bone marrow density (BMD) at lumbar (L)-spine
11/1/2013	Cazyva (cibrinzumab)	chronic lymphocytic leukemia (CLL)	✓		✓	Progression Free Survival (PFS)
11/13/2013	Imbruvica (ibrutinib)	mantle cell lymphoma (MCL)		✓	✓	Overall response rate (ORR)
11/22/2013	Glyso (simeprevir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
12/6/2013	Sovaldi (sofosbuvir)	hepatitis C genotypes 1, 2, 3 or 4	✓			Sustained Viral Response (SVR)
12/18/2013	Anoro Ellipta (irrelectinim and viamterol)	chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)
1/8/2014	Fanvga (dapagliflozin)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (HgA1C)
2/24/2014	Myalept (metreleptin)	leptin deficiency	✓		✓	Hemoglobin A1C (Hga1C)
4/15/2014	Tanzeum (albiglutide)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (Hga1C)
4/23/2014	Sylvant (situximab)	multicentric Castlemans disease (MCD) who are HIV and human herpes virus-8 (HHV-8) negative	✓		✓	Overall response rate (ORR)***
4/29/2014	Zykadia (ceritinib)	anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC)		✓	✓	Overall response rate (ORR)
7/3/2014	Seleodag (selinastat)	peripheral T-cell lymphoma (PTCL)		✓	✓	Overall response rate (ORR)
7/23/2014	Zydelig (idazalisce)	1) Chronic lymphocytic leukemia (CLL) 2) Follicular B-cell non-Hodgkin lymphoma (FL) and small lymphocytic lymphoma (SLL)	✓ ¹	✓ ²	✓	1) Progression Free Survival (PFS); 2) overall response rate (ORR)
7/31/2014	Silverdi Respimat (sibasteno)	Chronic obstructive pulmonary disease (COPD)	✓			Forced expiratory volume in 1 second (FEV1)

* For CLL indication
¹ For FL and SLL indications

Approval Date	Drug Name	Abbreviated Indication*	Traditional Approval	Accelerated Approval**	Orphan Designation	Surrogate Endpoint
8/1/2014	Jardance (moglitazone)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (Hga1C)
8/19/2014	Corselga (niglustat)	Type 1 Gaucher Disease	✓		✓	spleen volume
9/4/2014	Keytruda (pembrolizumab)	irresectable or metastatic melanoma		✓	✓	tumor response rate by computerized tomography (CT) and magnetic resonance imaging (MRI)
9/16/2014	Tivicity (tigatuzumab)	Type 2 Diabetes Mellitus	✓			Hemoglobin A1C (Hga1C)
10/10/2014	Havron (hepasvir and sofosbuvir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
10/15/2014	Esbriet (pirfenidone)	idiopathic pulmonary fibrosis (IPF)	✓		✓	Forced Vital Capacity (FVC)
10/15/2014	Ofev (nintedanib)	idiopathic pulmonary fibrosis (IPF)	✓		✓	Forced Vital Capacity (FVC)
10/29/2014	Thimerexa	prevention of meningococcal B infection		✓		immunogenicity
12/3/2014	Blinxto (blinatumomab)	B-cell precursor acute lymphoblastic leukemia (ALL)		✓	✓	Complete remission (CR) or complete remission with partial hematological recovery (CRP)
12/19/2014	Viekira Pak (ombitasvir / paritaprevir / Voxsolar / dasabuvir)	hepatitis C genotype 1	✓			Sustained Viral Response (SVR)
12/19/2014	Lynparza (olaparib)	advanced ovarian cancer with deleterious or suspected deleterious germline BRCA mutations		✓	✓	Objective response rate (ORR)
12/22/2014	Opdivo (nivolumab)	irresectable or metastatic melanoma		✓	✓	Objective response rate (ORR)

* Please see full indication in product labeling.
^{**} There were 36 total Accelerated Approvals (AAs) for 2010-2014 including new and supplemental NDAs and BLAs as well as AAs based on intermediate clinical endpoints. 18 of these 36 AAs were for novel NME drugs and orphan biologics approved using surrogate endpoints—these are listed in the table.
^{***} Approval determination relied upon a surrogate endpoint and a direct clinical benefit; only the surrogate endpoint is listed in the table.
Please note: The information provided in the table is preliminary and should be considered a work-in-progress, as there is no established definition for "surrogate endpoint" vs. "clinical outcome assessment".

The CHAIRMAN. Thanks, Dr. Woodcock. Dr. Shuren.

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

Dr. SHUREN. Mr. Chairman and members of the committee, thank you for the opportunity to testify today.

Medical technology is transforming the way America practices medicine and making a difference in patients' lives. Expediting patient access to new medical devices is critical but only if that technology is safe and effective. We know that unnecessary regulatory burden can drive innovators to seek more favorable environments, which can impact timely patient access to potentially lifesaving therapeutics.

We also know that lax oversight can lead to patient harm. Medical devices that have not been shown to be safe and effective can hurt American patients and can drive up healthcare costs.

In 2010, FDA's medical device program faced severe problems. Some consumer, patient, payer, and practitioner groups thought we weren't doing enough to assure patient safety, while industry felt that we had raised the safety and effectiveness bar too high and that we were taking far too long to review new device submissions. In fact, from 2000 to 2010, measures of device review performance showed steadily worsening performance year after year.

Recognizing the need to address these concerns and strengthen the device program, CDRH began to make systematic changes to our policies, processes, and management oversight. Since then, the performance of the device program has been steadily improving.

For example, since 2010, we've reduced the average total review time of 510(k)'s for moderate-risk devices by 10 percent and cut the number of pending submissions by about 30 percent. For PMAs for high-risk devices, we've cut the average total review time by 26 percent and are on track to reduce it by one-third, and we've cut the number of pending submissions by 43 percent.

For *De Novos*, a pathway for innovative lower risk devices, we've cut nearly 2 years off the review process and seen almost a doubling of *De Novo* requests. At CDRH, we have focused our strategic priorities on reducing the time and cost of bringing devices to market so that companies will bring their devices to the United States first while still meeting the U.S. safety and effectiveness standard.

One of our priorities is to strengthen the clinical trial enterprise. We've already reduced the median time to full approval of a clinical trial by almost 1 year and are poised to meet our goal of reducing the median time from 442 days to 30 days, and our first cycle approval times for clinical trials has increased ninefold.

We've recently launched a pathway for breakthrough devices called the Expedited Access Pathway program. This program provides manufacturers the opportunity to ship the collection of some data where we otherwise require premarket to the post-market setting. Post-market data includes information gathered as a part of routine clinical practice, such as through device registries and electronic health records. In fact, we are already relying on registry data to approve expanded device indications.

If our proposal for a national surveillance system for medical devices is fully implemented, we can further reduce premarket data requirements through greater reliance on post-market data collection and, just as important, improve patient safety. Last year, we created a multi-stakeholder planning board which included patients, practitioners, payers, and industry. The board recently released their recommendations for implementing the system.

CDRH also believes that patients should have a say in our review decisions. We've begun our initiative to utilize patient preference data in our review of a device's benefits and risks. Just recently, CDRH used such data in the approval of the first device to treat obesity since 2007.

Flexibility already built into the existing statutory framework for medical devices allows us to adapt to emerging technologies. For example, over the past few years, we decided to no longer oversee

many lower risk software medical devices we previously regulated. We recognize that our oversight is best suited for higher risk functions, and by removing our oversight in the low-risk digital area, we are able to help stimulate the development of health-related mobile apps.

In response to the emergence of next-generation sequencing platforms, we have leveraged data from curated data bases rather than require new clinical studies to help bring innovative tests to market. We recently proposed a new regulatory model for next-generation sequencing tests that would routinely rely on evidence generated by the clinical community rather than on company-sponsored clinical studies.

Today, the medical device program is in a better place to protect and promote public health than when I testified before you in 2011. But we know we still have more to accomplish.

It is my hope that whatever this committee decides to do—and we appreciate the opportunity to work with you—it does not impede the strong progress we have made nor lose sight of the tremendous effort and dedication of the medical device program staff and managers.

Mr. Chairman, I commend the committee’s efforts and I’m pleased to answer questions the committee has.

[The prepared statement of Dr. Shuren follows:]

PREPARED STATEMENT OF JEFFREY SHUREN, M.D., J.D.

Chairman Alexander, Ranking Member Murray, and members of the committee, I am Jeffrey Shuren, Director, Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA). I am pleased to be here today to discuss FDA’s work to promote patient access to innovative medical devices while ensuring appropriate patient protections.

INTRODUCTION

Advances in medical technology are transforming established medical practice and bringing completely new models of treatment, prevention, and diagnosis to patients right now. New devices include not only improvements over existing technology—devices that make less-invasive treatments possible and provide new options to patients whose condition would have been considered untreatable in the past—but also technologies that will be keystones in emerging fields, such as precision medicine. Genetic testing offers the promise of targeting the right treatment to the right patients, reducing ineffective treatment decisions, and speeding the delivery of therapies that work. Health information technology can empower people with chronic diseases to manage their own health and well-being by putting medical “apps” right into the hands of patients. FDA has responded to the promises—and challenges—posed by these devices with flexible, risk-based approaches to its oversight role and with strong performance in bringing new, safe and effective products to market.

At the same time, FDA needs to ensure it is delivering on its oversight role. This role requires that FDA facilitate patient access to new medical technology while providing the oversight to minimize unnecessary risks and ensure devices provide clinical benefit. At one end of the spectrum, unnecessary regulatory burden could drive innovators to seek more favorable environments, potentially depriving American patients of timely access to needed therapeutic and diagnostic devices. At the other end of the spectrum, lax oversight could lead to patient harm from devices that have not been tested and shown to be safe and effective, and affect the marketplace by reducing confidence in the health care system that devices will do what they are intended to do without harming the patients they are intended to benefit. A flexible, risk-based approach to oversight of medical technology is critical to striking the right balance.

FDA’s existing framework establishes flexibility that has allowed FDA to develop innovative approaches to medical device oversight, approaches that reduce unnecessary burden without compromising assurances that devices marketed to American patients are safe and effective. Improvements to FDA’s device program have already

resulted in decreased review times and timely patient access to important new devices. And while other changes are too new to evaluate, early signs are positive and point to additional improvements in timely access for U.S. patients to safe and effective devices.

Glossary of Key Terms

510(k)—An application to FDA for market clearance of Class II devices and a small number of Class I devices. The manufacturer must demonstrate that the device is “substantially equivalent” to a legally marketed device. FDA currently reviews 510(k)s for fewer than 10 Class III devices that were legally marketed before 1976. FDA is in the process of reclassifying or finalizing calls for PMAs for these devices.

De Novo—A premarket request for FDA to classify a novel device into Class I or Class II.

IDE—Investigational Device Exemption: An application to conduct studies on human subjects.

MDUFA—Medical Device User Fee Act: An agreement between FDA and industry that FDA will take certain actions and attain performance goals in exchange for industry user fees.

PMA—Premarket Approval Application: The application to FDA for Class III devices. The manufacturer must demonstrate a reasonable assurance of safety and effectiveness to gain approval of a PMA.

THE U.S. REGULATORY ENVIRONMENT FOR DEVICES: 2010–15

Performance of FDA’s Device Program

In the early part of this decade, many policymakers and FDA stakeholders called for reform of FDA’s device program, arguing that FDA regulation was driving companies to relocate overseas or market their devices abroad before introducing them in the United States. To support their arguments, critics pointed to contemporary surveys of device manufacturers and FDA’s own data showing a decline in the performance of its premarket program from 2000 to 2010. Although FDA raised questions about the methodology used in some of these studies,¹ the underlying premise that industry’s perception of FDA oversight can affect decisions about introducing new technology in the U.S. marketplace is important. This premise, as well as FDA’s own awareness of the Agency’s worsening performance numbers, moved FDA to implement a number of new policies and programmatic changes over the past 5 years to improve its performance and to adapt its oversight to the global marketplace, and to new technologies. Added funding and increased capacity, as the result of the 2012 reauthorization of MDUFA also helped reverse the direction of the Agency’s medical device premarket program.²

Today, the performance of FDA’s device program has significantly improved. FDA is on track to meet all of its MDUFA performance goals related to device review, and premarket performance measures of FDA’s device program show marked improvement since the start of the current decade on several measures related to how quickly devices come to market in the United States.

FDA is making progress in bringing down total review times for 510(k) submissions, *de novo* requests, IDEs, and the higher risk PMA applications. While data is not complete for the years 2013 and 2014 because some applications remain open, existing data show improvements on several important measures:³

- Time to decision on device submissions has decreased:
- **510(k)s**: The vast percentage of device premarket submissions received by FDA in any given year are 510(k)s. In fiscal year (FY) 2010, it took 116 days for a total time to decision on a 510(k). By fiscal year 2014, total time had

¹These arguments often rely on studies published early in this decade to support these assertions—the methodology of which FDA has questioned. See Letter from Jeanne Ireland, Assistant Commissioner for Legislation, FDA, to Ranking Member Henry A. Waxman (July 11, 2011) <http://democrats.energycommerce.house.gov/sites/default/files/documents/Waxman-FDA-Concerns-Regarding-Makower-Study-of-Medical-Device-Regulation-2011-7-18.pdf>.

²FDA estimates that it has added at least 190 of the planned 240 staff authorized by MDUFA III, since the end of fiscal year 2011. These additional staff members have contributed to FDA achieving the new performance goals under MDUFA III.

³Appendix A provides additional data showing the current performance of FDA’s device program, including data over several years that show the course of improvement over the past 5 years.

dropped by 10 percent to about 105 days (these figures compare review times when 75.8 percent of submissions are closed).

- **PMAs:** Original PMAs generally account for only about 1 percent of all device applications received by FDA. Average total time to decision in fiscal year 2014 has decreased to 236 days from 320 days at its peak in fiscal year 2009, or an improvement of 26 percent (these figures compare review times when 41 percent of applications are closed). Once all fiscal year 2014 applications are closed, we project performance will meet or exceed fiscal year 2012 levels, which would be at least a 32 percent improvement since 2009.
- **IDEs:** Median total time to full IDE approval decision has decreased from 442 days in fiscal year 2011 to 101 days in fiscal year 2014, reducing the time it takes to bring a new medical device to market by nearly a full year. The number of IDE studies requiring more than two cycles to full approval has been reduced by 34 percent.
- **De novo:** The average total time to final decision for *de novo* requests (510(k) plus *de novo* review) submitted after a device was found to be not substantially equivalent through the 510(k) process has been reduced from 992 days in fiscal year 2010 to 300 days in fiscal year 2014.
- Another measure of the performance of the medical device program is that FDA is working with industry to ensure that submissions are complete and ready for review. As a result, the percentage of submissions that are cleared and approved has increased since 2010:
 - The percentage of 510(k)s cleared increased from 73 percent to 84 percent.
 - The percentage of PMAs approved increased from 59 percent to 86 percent.
- The number of pending submissions at the end of a year has significantly decreased since 2010:
 - The number of 510(k) submissions has been reduced by 30 percent.
 - The number of PMA submissions pending has been reduced by 43 percent.

Our experience also suggests that there is marked improvement in the medical device industry's perception of FDA. In 2014, CDRH made providing excellent customer service a strategic priority and launched an effort to improve customer service that included staff training, surveys to assess interactions with customers and measure customer satisfaction, and, based on feedback from customers, actions to improve the quality of CDRH actions and services. CDRH's 2014 results show 83 percent satisfaction. While customers include everyone who interacts with FDA's medical device program, CDRH's results generally appear to track our experience.

FRAMEWORK FOR DEVICE OVERSIGHT

The basic framework under which FDA oversees devices was put in place almost 40 years ago, when Congress enacted the Medical Device Amendments of 1976 (MDA). The MDA established a flexible framework for FDA's oversight of medical devices and required that FDA tailor its oversight of devices to the degree of risk presented. Although the framework established under the MDA recognizes that medical devices inherently carry risk, the MDA did not mandate that FDA eliminate risk. Rather, FDA applies only the level of oversight necessary to establish a reasonable assurance of safety and effectiveness for devices. Under this framework, only about half of all devices are subject to any premarket review by FDA, and, of the devices that are subject to premarket review, FDA reviews clinical data for fewer than 20 percent because there are other, less-burdensome means to determine that there is a reasonable assurance that a device is safe and effective.⁴

FDA oversight of devices is tailored to three risk-based classifications:

- **Class I, or low-risk devices:** FDA does not review any premarket information for Class I devices, with the exception of a small subset of Class I "reserved" devices. Class I makes up about 50 percent of all medical devices. An example of a Class I device is an elastic bandage.
- **Class II, or moderate-risk devices:** FDA generally reviews 510(k) submissions for these devices, which requires a demonstration of substantial equivalence to a legally marketed device. About 80 percent of all 510(k)s contain only non-clinical data. Examples of Class II devices include glucose test strips and infusion pumps.
- **Class III, or high-risk devices:** FDA generally reviews PMAs containing clinical and non-clinical data to determine whether there is a reasonable assurance of

⁴The 20 percent includes in vitro diagnostics (IVD) devices, which typically contain test results based on human-derived samples. When IVDs are excluded, the number of submissions with clinical data drops to fewer than 10 percent.

safety and effectiveness for these devices. FDA generally reviews about 40 PMAs a year. Examples of PMA devices include heart valve replacements and diagnostic tests used to select ovarian cancer patients for a drug regimen.

FDA's evidentiary standard for premarket review of devices is valid scientific evidence, a standard established by Congress in 1976 that still sets the benchmark for evidence to support premarket submissions. This benchmark ensures that the evidence is of sufficient quality that it can be relied on to determine whether or not a device should be approved or cleared. Although valid scientific evidence includes randomized-controlled clinical trials, the overwhelming majority of devices come to market based on non-clinical data, small clinical studies, or both. The valid scientific evidence standard encompasses many other forms of evidence, such as bench testing, journal articles, observational data, and foreign studies.

In vitro diagnostic (IVD) devices have been regulated by FDA under its risk-based device framework since the inception of the device program. Diagnostic tests can be used in the context of acute outbreaks, such as the recent Ebola outbreak, and in the diagnosis and treatment, including management, of chronic diseases like cancer and diabetes. Success in combating these diseases depends on diagnostic tests that can accurately detect them and be used to select and manage treatments. A case in point is the widespread use of glucose meters and diabetes test strips. These devices can empower people with diabetes to manage their diseases independently, but only when the devices are accurate. In recent years, test reports of falsely high and low blood sugar levels have led to multiple recalls of these products over concerns that false readings could lead to incorrect treatment decisions; in particular, insulin administered in response to falsely high measures of blood sugar could lead to acute hypoglycemia, coma, and even death, if left untreated. The American Diabetes Association issued a statement of strong support of FDA oversight of these tests, stating:

The American Diabetes Association strongly endorses [FDA] oversight of test strip manufacturers[.]. The Association applauds the FDA's requirements that all test strips meet existing FDA standards for medical devices, since those standards are designed specifically to require the greatest accuracy in readings when an error would place a patient's health and life in danger.⁵

For IVD devices, a reasonable assurance of safety and effectiveness means that a test has analytical and clinical validity. "Analytical validity" assesses how well the test detects or measures certain markers in human specimens. "Clinical validity" assesses whether the marker has clinical significance, such as correlation with disease or the ability to predict a therapeutic response to a drug. As FDA's recent announcement—that it intends to exempt carrier screening tests from premarket review—shows, the level of data FDA requires to show analytical and clinical validity for IVD devices depends largely on risks from the device.

The central features of FDA's device program—a risk-based framework that tailors oversight to device risk; a flexible review standard that requires a reasonable assurance of safety and effectiveness; and an adaptive but scientifically grounded evidentiary standard of valid scientific evidence—have served the public well. While there have been multiple amendments to FDA's original authority, providing new premarket pathways and enhancing FDA's post-market oversight, the framework put in place by the MDA continues to provide the tools to assure safety and effectiveness of therapeutic and diagnostic devices while allowing FDA to adapt its oversight to the demands of rapidly evolving medical technology.

ADAPTING FDA'S OVERSIGHT ROLE TO CURRENT CHALLENGES: 2010–15

The new policies and programmatic changes FDA has implemented in the past 5 years respond to the needs of American patients to have timely access to high-quality, and safe and effective devices, and to challenges created by rapidly evolving fields of medical innovation. These initiatives have had far-ranging objectives, from providing FDA review staff with new tools to assess the benefits as well as the risks of a device to American patients to promoting regulatory certainty and empowering patients to manage their well-being. Among these initiatives are process improvements and policy changes to its oversight of clinical investigations of devices.

Streamlining Clinical Trials

In 2014, FDA established a Clinical Trials Program to coordinate its oversight of clinical studies of devices; provide interventions if a review of an application to conduct a clinical investigation of a device (Investigational Device Exemption or IDE) takes more than one cycle; offer more opportunities for interactions with sponsors; expand training for review staff; and establish new or modified policies in this area.

⁵http://professional.diabetes.org/News_Display.aspx?CID=93129.

For example, recognizing that devices that are studied in the United States in the early stages of clinical assessment are more likely to reach U.S. patients sooner in pivotal trials and as marketed devices, FDA implemented a pilot program in 2011 to encourage early feasibility studies, or early stage clinical studies, of devices in the United States. In 2013, FDA issued final guidance on early feasibility studies;⁶ under this program, FDA may accept a higher degree of uncertainty during the device development process to facilitate important early clinical evaluation of promising technologies. As a result, we are beginning to see an increase in companies submitting IDEs for early feasibility studies in the United States and more approvals of such IDEs. In the past 2 years, we have reduced the median time to approval for early feasibility studies by 70 percent, from 226 days in fiscal year 2013 to 66 days in fiscal year 2015.

Devices that are studied in the United States in the early stages of development are more likely to reach U.S. patients sooner in pivotal studies and as marketed devices. In the past 15 fiscal years, for those original PMAs whose approval was based on FDA-approved pivotal clinical studies, 94 percent (283 out of 300) of these approvals were based on a single pivotal clinical study. More recently, in the past 5 years, the number has increased to 98 percent (82 out of 84). Of the 82 FDA-approved original PMAs whose approval was supported by a single pivotal clinical study, 32 (39 percent) included studies enrolling subjects outside of the United States. For IVD devices, where clinical studies are typically conducted in at least three sites, sponsors generally choose to have one of those sites inside of the United States to address differences between the United States and other countries in how medicine is practiced, patient populations, and disease progression.

FDA is facilitating and encouraging the use of innovative clinical trial designs and statistical methods such as adaptive clinical trials and Bayesian statistics. By incorporating existing clinical information about devices into statistical analyses, adaptive clinical trials such as the Bayesian approach can support a marketing application for a device based on shorter and smaller clinical trials. In 2010, FDA published a guidance document on how Bayesian methods can be used to design and analyze data from medical device clinical trials.⁷ FDA's efforts to promote the appropriate use of adaptive trial designs to support premarket device applications date to the late 1990s⁸ and in recent years, many devices have come to market based on adaptive trial designs. For the period from 2007 to May 2013, FDA received 250 submissions that were adaptive, most of which were pre-submissions and IDEs. About 30 percent of these used Bayesian methodologies. In addition, there were 17 PMAs and PMA Supplements that used adaptive clinical trials from 2007 to May 2013, eight of which used Bayesian methodologies.

These programmatic improvements and policy changes have already yielded results in significantly reduced time to approval of IDEs and increasing approval rates. While the full effect of these programmatic improvements on U.S. health care will not be known for several years, streamlined processes for initiating device studies in the United States and reductions in the time to approval for U.S. clinical studies are promising developments in the effort to ensure U.S. patients have timely access to medical devices of public health importance.

Flexible decisionmaking

In recent years, FDA has also implemented a series of new premarket policies that build on the risk-based framework established by the MDA. While these policies are relatively new, and the programmatic effects cannot yet be measured, many of the policies have affected important review decisions, impacting public health by speeding access to new safe and effective devices.

Benefit-Risk: FDA's standard for premarket review of high-risk devices has always required the Agency to weigh the benefits of a device against its risks. For the past 3 years, however, FDA has used a more flexible, patient-centric, and transparent benefit-risk framework to evaluate devices. Under this framework, developed

⁶*Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies: Guidance for Industry and FDA Staff* (October 1, 2013), available at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/documents/ucm279103.pdf>.

⁷*Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials* (February 5, 2010), available at <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidance/documents/ucm071072.htm>.

⁸Gregory Campbell (2011) Bayesian Statistics in Medical Devices: Innovation Sparked by the FDA, *Journal of Biopharmaceutical Statistics*, 21:5, 871–87, DOI: 10.1080/10543406.2011.589638. This article refers to 16 approved PMAs that relied on Bayesian analysis and one cleared 510(k); there have been several additional device approvals since 2011, but an exact number is not available.

with public feedback, reviewers weigh a number of factors to arrive at a decision of whether the benefits of a device outweigh its risks, including: the type, magnitude, and duration of a risk or benefit, the probability that a patient will experience the risk, patient tolerance for risk, availability of alternative treatments, and the value the patient places on treatment. Under this approach, devices that present a small but real likelihood of preventing serious disability or death could, with appropriate risk mitigation such as labeling, reach the market despite greater uncertainty about its risks. Also, in appropriate cases, FDA may defer some data otherwise collected premarket to the post-market setting to promote timely access to the benefits of devices of public health importance, provided there is still a reasonable assurance of safety and effectiveness. FDA currently applies this benefit-risk framework to all reviews of high-risk and novel lower-risk devices.⁹

Patient Preferences Initiative: Increasingly, patients seek to be involved in decisionmaking about their own health. Recognizing the importance of considering patients' views in deciding how the probable risks and benefits of medical technology should be weighed, in 2013 FDA launched the Patient Preferences Initiative. The initiative seeks to incorporate valid scientific evidence of patient preferences on the benefit-risk tradeoffs of medical devices into premarket review and other decisionmaking by FDA's device program. For example, a team of FDA scientists published an article with leading behavioral economists, illustrating how patient preferences can inform medical device approval decisions.¹⁰ The authors successfully tested a new method for capturing patient sentiment and translated it into a decisionmaking tool for incorporating patient preferences into clinical trial design for obesity treatments. They were able to estimate the tradeoffs in risks that obese patients are willing to accept in exchange for a certain amount of weight loss, and the minimum number of pounds they would have to lose to tolerate the risks of a weight-loss device. FDA used the results of this study to inform the product approval decision.

Use of Patient Preferences to Approve a New Weight-Loss Device

In 2015, FDA approved a new weight-loss device—the *Maestro Rechargeable System*, a new therapeutic option for certain obese patients. The decision to approve the device was based in part on the patient preference data, which showed that a substantial portion of obese patients would accept the risks associated with a surgically implanted device if they lost a sufficient number of pounds. *Maestro* is the first FDA-approved obesity device since 2007.

Expedited Access Program: In 2014, FDA proposed a program for expedited patient access to devices that are of potential significant public health benefit because they are intended to treat or diagnose patients with life-threatening or irreversibly debilitating conditions whose medical needs are unmet by current technology—what some have called “breakthrough devices.” Under this program, FDA would provide earlier and more interactive engagement with sponsors of such devices, including the involvement of senior management and a collaboratively developed plan for collecting the scientific and clinical data to support approval—features that, taken together, should provide patients with earlier access to safe and effective medical devices. The program would target devices with potentially high impact on patient health because, for example, they fulfill an unmet need by offering an important advantage over existing devices. To promote earlier patient access, some data collection for devices marketed under this pathway might be moved from pre- to post-market, provided there is still a reasonable assurance of safety and effectiveness concerning the device. FDA issued final guidance¹¹ in April 2015. The Expedited Access Pathway program went into effect on April 15, 2015.

REGULATORY SCIENCE: NEW USES OF EVIDENTIARY AND ANALYTICAL TOOLS

FDA has also invested in several new regulatory science programs over the past several years to reduce the time and cost but not the quality of data development for devices. These programs promote the development and use of tools, analytical methods, and data sources in premarket applications to bring safe and effective devices to market faster and at less cost.

⁹ *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* (March 28, 2012), available at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm296379.pdf>.

¹⁰ Marin P. Ho, et al., *Incorporating Patient-Preference Evidence into Regulatory Decision-Making, Surgical Endoscopy* DOI 10.1007/s00464-014-4044-2 (2015).

¹¹ <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>.

Medical Device Development Tools (MDDTs)

An MDDT is a scientifically validated tool—a clinical outcome assessment (e.g., patient-reported or clinician-reported rating scales), a test used to detect or measure a biomarker, or a non-clinical assessment method or model (e.g., an *in vitro*, animal, or computational model) that aids device development and regulatory evaluation. In August, 2014, FDA announced a pilot program under which anyone can submit scientific information to FDA to “qualify” an MDDT. Once qualified, MDDTs can be used to support premarket applications. In practice, this can enable sponsors to support a PMA, *de novo* request, or a 510(k) using smaller and shorter clinical trials. The MDDT program builds on FDA’s successes, developing computational models like the Virtual Family (VF), a set of highly detailed, anatomically correct, computational whole-body models, designed to mimic humans of both sexes at various stages of growth.

Regulatory Science—The Virtual Family (VF)

FDA collaborated with researchers and industry to create the VF, a set of four highly detailed, anatomically correct whole-body models of an adult male, an adult female, and two children. Currently, the VF models are used for electromagnetic, thermal, acoustic, and computational fluid dynamics (CFD) simulations—simulations that can supplement or replace data from clinical investigations of devices. At the end of 2014, the VF was used in more than 120 medical device submissions to FDA and was cited more than 180 times in peer-reviewed literature. Recently the Virtual Population 3.0 became available. The VF are available free of charge to researchers for use in device development.

Medical Device Innovation Consortium (MDIC)

In 2012, FDA and LifeScience Alley (a biomedical trade association) co-founded a new nonprofit partnership—the Medical Device Innovation Consortium—the first public-private partnership (PPP) whose mission is to advance medical device regulatory science. MDIC is a collaboration among Federal agencies, industry, nonprofit organizations, and patient advocacy organizations, and provides a venue for leveraging of resources, people, and intellectual capital to find solutions to common challenges in the precompetitive space. MDIC supports the development of non-clinical device development tools that can reduce the need for or size of clinical studies to support market approval as well as steps to reduce the time and cost of clinical trials. MDIC has several active project focus areas, including the following:

- **Patient-centered Benefit-Risk:** This project focuses on developing scientifically robust ways to measure patient perspectives on the benefits and risks of medical devices, and a framework for incorporating patient perspectives into device development and regulatory decisionmaking.

- **Clinical Trials Innovation and Reform:** MDIC is working with FDA, NIH, industry, academia, and patient groups to explore ways to improve the efficiency and cost-effectiveness of medical device clinical trials while maintaining data quality. The goal is to streamline the clinical trial process and restore the United States to the country of first choice to conduct clinical research for medical technology innovation. The project aims to innovate and reform the U.S. clinical trial process by defining and tackling top barriers to efficient design and conduct of medical device clinical trials.

- **Computer Modeling & Simulation:** The goal of this project is to reduce the time and cost of bringing devices to market while improving patient safety by advancing the science around computer modeling and simulation for medical devices. These models, when of sufficient quality to be considered “regulatory grade,” can be used to assess device performance, thus reducing or obviating the need for other more expensive or burdensome types of scientific evidence (such as human clinical studies).

MDIC’s collaborations focus on advancing regulatory science to propel device development through the regulatory process and to market, resulting in smarter regulation and earlier patient access to safe, effective, and high-quality devices.

REAL-WORLD DATA

In September 2012, FDA published a report, “Strengthening Our National System for Medical Device Postmarket Surveillance,” which proposed a National Medical Device Surveillance System (MDS) for improving and addressing the limitations of our current system for monitoring medical device safety and effectiveness. This report recommended establishing a national infrastructure for gathering and analyzing real-world data, or data collected as part of routine clinical practice and patient experience. The purpose of such a national system is to identify potential safe-

ty signals in near real-time; better understand the benefit-risk profiles of medical devices on the market; and facilitate the clearance and approval of new devices, or new uses of existing devices.

In the past year, FDA has achieved tremendous progress laying the groundwork for the MDS. FDA has begun implementing the unique device identification (UDI) rule for the highest risk devices, including development of a Global UDI Data base (GUDID) as the repository for information that unambiguously identifies devices through their distribution and use. By promoting incorporation of UDIs into electronic health information (such as electronic health records, or EHRs, and device registries), a vast quantity of untapped real-world data from clinical experience with devices housed in EHRs and other electronic information sources may become available for use in understanding the benefit-risk profiles of medical devices. In addition, FDA continues to build registry capabilities both domestically (such as the National Breast Implant Registry) and internationally (such as the International Consortium of Vascular Registries). FDA established a Medical Device Registry Task Force consisting of key registry stakeholders as part of the Medical Device Epidemiology Network (MDEpiNet) Program, a collaborative program that FDA co-founded to develop new and more efficient methods to study medical devices and to enhance FDA's ability to more fully understand the safety and effectiveness of medical devices after they are marketed. FDA commissioned the Engelberg Center for Health Care Reform at the Brookings Institution to convene and oversee deliberations of the Medical Device Postmarket Surveillance System Planning Board. In February 2015, the Planning Board issued a report, "Strengthening Patient Care: Building an Effective National Medical Device Surveillance System," outlining recommended steps toward the development, oversight, and effective use of medical devices, while supporting improvements in patient safety and health outcomes.

FDA's work in developing registries has relieved post-market burden by allowing device sponsors to submit data from registries instead of conducting their own new post-market studies. FDA is also pursuing strategies to use data from the most robust registries in the premarket context, and has already relied on registry data to expand access to transcatheter aortic valve replacement devices.

Use of Real-World Evidence to Expand Use of Minimally Invasive Heart Valve Replacement

Before 2014, transcatheter aortic valve replacement, a minimally invasive alternative to open heart surgery, was indicated only for patients with aortic stenosis for whom open heart surgery was too risky, who were yet healthy enough to undergo certain placement procedures. At the same time, clinical experience indicated this device could offer good outcomes to inoperable patients with no other options. In 2014, FDA expanded approval for the Edwards Sapien® Transcatheter Aortic Valve Replacement to patients deemed inoperable without requiring controlled clinical trials of the new use. FDA approved the expanded indication based on registry data from clinical use of the device.

Adapting to New Technology

FDA's device program aims to be adaptive in responding to new technologies. Recent policies have focused FDA oversight of health IT on medical devices that present greater risks, with the goal of permitting access to a range of products while ensuring the safety and effectiveness of medical devices—a subset of mobile medical apps that present a greater risk to patients if they do not work as intended—such as those that provide or assist health care practitioners with treatment and diagnosis. FDA's device program is leading the development of clear, streamlined pathways for technologies that are pivotal to the success of precision medicine, such as companion diagnostics and Next-Generation Sequencing devices. The approach to oversight in these areas demonstrates the adaptability of the existing regulatory framework.

- **Mobile Medical Applications and Other Health IT:** As the number and functionality of mobile applications, or apps, exploded in recent years, in 2013, FDA announced a policy under which FDA intended to focus its regulatory oversight on those mobile medical apps that pose the greatest risk to consumers and exercise enforcement discretion for the majority of mobile apps as they pose minimal risk to consumers. FDA followed this policy with a preliminary health IT report produced in collaboration with the Office of the National Coordinator and the Federal Communications Commission, as required by the Food and Drug Administration Safety

and Innovation Act (FDASIA) of 2012;¹² this report outlines a series of recommendations and actions for the public and private sectors to take in this dynamic area of health IT to avoid duplicative regulation, while promoting innovation and protecting patient safety. The agencies accepted public comment on this report to inform its development. Recently, FDA has issued guidance under which FDA clarified that it intends to exercise enforcement discretion for medical device data systems,¹³ a form of health IT that, while low risk, is widely used in the delivery of health care. With these actions, FDA helped to make clear the narrow arena of health IT where the Agency intends to continue its oversight—namely, the space occupied by the riskiest forms of medical software—while clearly stating its intention to not focus its oversight over a broad range of other medical device software products.

FDA recently proposed a similar policy for all low-risk devices used to promote health and well-being and to help individuals with chronic disease maintain wellness. The policy extends to products used to promote physical fitness, maintenance of a healthy weight, relaxation, and similar states of well-being, so long as the product does not present inherent risks to users. As with FDA's recent policies concerning health IT, FDA proposed this policy to provide greater certainty to product developers and users that FDA intends to focus its oversight in these emerging areas of product development on medical devices that present more than low risk.

- **Companion Diagnostics:** Companion diagnostic tests play an important role in promptly determining which therapies are safe and effective for a particular patient and are a key component of precision medicine. FDA has approved 20 companion diagnostic tests, all of them within the PDUFA performance goals for the corresponding drug or biological product, ensuring the timely marketing authorization of both. In 2014, FDA issued guidance¹⁴ describing a clear marketing pathway for developers of companion diagnostic tests and pharmaceutical manufacturers, receiving strong support from both pharmaceutical and conventional test manufacturers for providing regulatory clarity in this rapidly advancing area of medicine. Companion diagnostics approved by FDA in recent years include the BRACAnalysis CDx™ test, a laboratory-developed test that aids in determining which ovarian cancer patients are more likely to respond to the drug Lynparza™ (olaparib), based on certain BRCA variants; the THxID™ BRAF Kit, which detects certain mutations in melanoma tissue samples to aid in selecting patients for drug therapy with Tafinlar® (dabrafenib) or Mekinist™ (trametinib); and the *therascreen*® KRAS RGQ PCR Kit, a test that screens out colorectal cancer patients with genetic mutations known to predict a nontherapeutic response to the biological products Erbitux® (cetuximab) and Vectibix® (panitumumab).

- **Next-generation Sequencing:** Many newly developed genomic diagnostic tests rely on next-generation sequencing (NGS), an advanced technology, which is becoming a keystone of precision medicine. NGS tests can rapidly generate an unprecedented amount of genetic data for each patient. Most IVD devices are used to detect a single or a defined number of markers to diagnose a limited set of conditions; in contrast, a single NGS test can identify thousands or millions of genetic variants that can be used to diagnose or predict the likelihood of an individual developing a variety of diseases. FDA has provided marketing authorization for an NGS test for cystic fibrosis using innovative approaches to establishing the test's effectiveness. As part of the President's Precision Medicine Initiative FDA will develop a new approach for evaluating Next Generation Sequencing 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.

Next-generation Sequencing: Cystic Fibrosis (CF)

FDA authorized marketing for the Illumin MiSeqDx Cystic Fibrosis System *in vitro* diagnostic test, which detects 139 genetic mutations that are relevant to whether an individual will develop CF or transmit the CF genetic mutation to his or her children. FDA worked with the test developer to apply novel approaches to establishing clinical validity by using publicly available, quality-weighted human

¹² See FDASIA Health IT Report (April 2014), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM391521.pdf>.

¹³ *Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices: Guidance for Industry and FDA Staff* (February 9, 2015), available at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm401996.pdf>.

¹⁴ *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff* (August 6, 2014), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>.

reference genomes (databases) that were created through collaboration between FDA and the National Institutes of Standards and Technology (NIST), and analytical validity by using data showing the test could accurately detect a representative sample of variants,

FDA recently published a white paper outlining a possible approach to review of this technology that would greatly reduce burden by leveraging data in existing high-quality curated genetic data bases as an alternative to conducting new clinical trials and by reviewing analytical performance for only a subset of variants. FDA has received positive feedback from thought leaders in this area for identifying ways to adapt its review practices to this important new technology.¹⁵

CONCLUSION

This is a time of remarkable advances in medical device technology, advances that can extend lives, and minimize suffering for American patients. New technologies hold out promise for empowering patients in their own health care decisionmaking and for delivering precision treatments that are truly targeted to individuals. At the same time, the promise of advances in medical technology will only be realized if the patients and providers who use them are confident that they are safe and can do what they are intended to do.

FDA's device program has evolved alongside changes in medical technology and in the global marketplace. FDA has implemented several new policies and programmatic improvements to ensure American patients have timely access to devices without compromising standards of safety and effectiveness. Devices are coming to market more quickly, and more devices that go through FDA's premarket program are being approved and cleared for marketing. In addition, FDA has made its review of investigational devices more efficient and expeditious, streamlining the pathway to conducting clinical investigations in the United States.

The improvements in FDA's device program have occurred under a long-standing framework that tailors FDA oversight to a device's risks and benefits. This framework provides flexibility to adapt to new technology and to consider a variety of different forms of evidence. At the same time, the framework establishes a standard for devices marketed to American patients: there must be a reasonable assurance of safety and effectiveness for devices, demonstrated by valid scientific evidence. We believe this framework serves the public well, allowing FDA to meet the demands of rapid innovation and a changing global marketplace, while promoting public confidence in high-quality, safe, and effective devices.

Thank you for the opportunity to testify today about the steps FDA is taking to foster innovation. I am happy to answer questions you may have.

Appendix A. Medical Device Premarket Program Performance

MDUFA III

Performance Goals: Preliminary data for MDUFA performance goals through September 30, 2014, indicate that FDA is on track to meet all of its performance goals while maintaining a high workload. In fiscal year 2014, FDA received over 6,000 submissions for PMAs, PMA supplements, 510(k)s, *de novos*, and HDEs.

The *4th quarter MDUFA III Performance Report* presents preliminary performance for the fiscal year 2013 and fiscal year 2014 MDUFA III submissions. Further details can be found in the MDUFA III Quarterly Performance Reports available on FDA's *MDUFA III website*. (**Table 1**)

¹⁵Lander, Eric S., Cutting the Gordian Helix—Regulating Genomic Testing in the Era of Precision Medicine, *NEJM* 2015, DOI: 10.1056 p. 150.

¹⁶**Current** Performance presents the percentage of actions that FDA completed within the review-time goal as of September 30, 2014.

¹⁷**Review Progress** presents the number of submissions that had actions taken in fiscal year 2014, plus submissions pending but overdue as of September 30, 2014, whether or not they met the MDUFA goal date, out of all MDUFA cohort submissions.

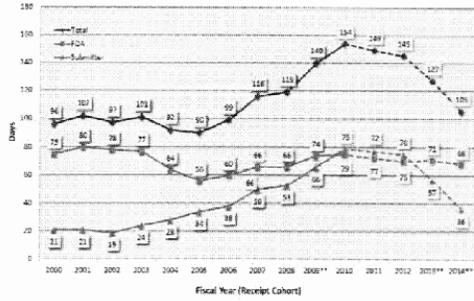
Table 1.— Fiscal year 2014 MDUFA III performance for selected submission types, as of September 30, 2014.

	Performance Goal [In percent]	Current Performance ¹⁶ [In percent]	Review Progress ¹⁷ [Percent complete]
PMA, Panel-Track PMA Supplements, and Premarket Reports:			
Substantive Interaction	75	95	37 of 45 (82 percent)
Decision with no Advisory Committee input	80	100	7 of 43 (16 percent)
Decision with Advisory Committee input	70		0 of 2
180-Day PMA Supplements:			
Substantive Interaction	75	94	127 of 178 (71 percent)
Decision	90	100	78 of 178 (44 percent)
Real-Time PMA Supplements:			
Decision	90	99	272 of 333 (82 percent)
510(k) Premarket Notifications:			
Substantive Interaction	75	97	2,739 of 3,166 (87 percent)
Decision	93	99	1,811 of 3,133 (58 percent)
CLIA Waivers:			
Substantive Interaction	95	100	14 of 14 (100 percent)
Decision for dual submissions ((510(k) and CLIA waiver)	90		0 of 1 (0 percent)
Decision with no Advisory Committee input	95	100	8 of 14 (57 percent)
Decision with Advisory Committee input	95		0 of 0

PREMARKET NOTIFICATION (510(K)) PROGRAM

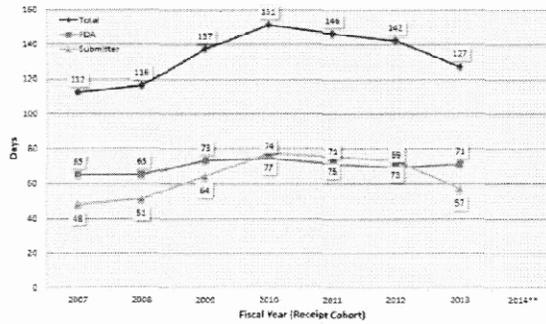
Average Time to Decision for 510(k)s: Total time to decision includes the time spent by FDA reviewing the application as well as the time spent by the submitter responding to questions from FDA. 510(k) average total time to decision has decreased since its peak in fiscal year 2010. (**Chart 1**) fiscal year 2013 and fiscal year 2014 cohorts are not yet fully closed; as of December 31, 2014, the fiscal year 2013 510(k) cohort was 99.2 percent closed and 2014 cohort was 75.8 percent closed. Comparison of receipts cohorts at the same closure¹⁸ levels show a 16 percent decrease in total review time (**Chart 2**) between fiscal year 2010 and fiscal year 2013 and a 10 percent decrease in total review time between fiscal year 2010 and fiscal year 2014. (**Chart 3**) The fiscal year 2013 cohort had the same average total time to decision as fiscal year 2014 at the 75.8 percent level of closure.

¹⁸Use of closure level provides a means for fair “apples to apples” comparisons, as performance is compared using the same percentage of work completed in a given year.



****Cohorts still open; percentage of cohort closed: FY 2009 = 99.9%, FY 2013 = 99.2%, and FY 2014 = 75.8%—average times will increase.**

Chart 1. Average time to decision for 510(k) receipt cohorts as of December 31, 2014. Includes SE and NSE decisions only; times may not add to total due to rounding.



****FY 2014 cohort is not yet 99.2% closed (as of December 31, 2014)**

Chart 2. Average time to decision for 510(k). Comparison of receipt cohorts when 99.2 percent closed. SE and NSE decisions only; times may not add to total due to rounding.

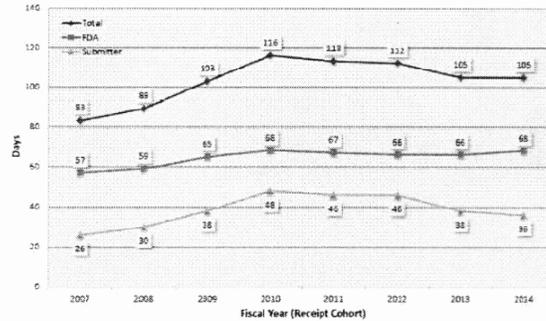
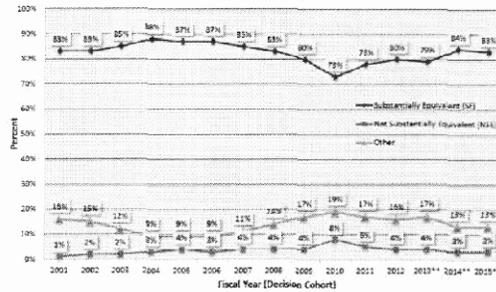


Chart 3. Average time to decision for 510(k).
 Comparison of receipt cohorts when 75.8 percent closed. SE and NSE decisions only; times may not add to total due to rounding.

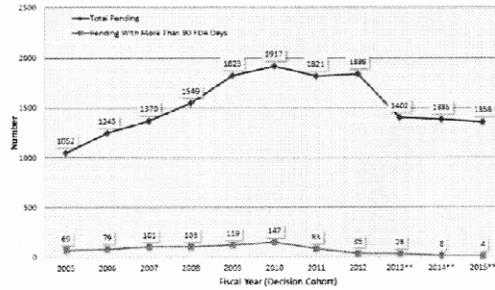
Organizationally, CDRH medical device premarket review offices are divided into review divisions, which are comprised of review branches. FDA is also closing the gap between the premarket review branches with the fastest and slowest review times. In 2003, the lowest performing branch reached 34 percent of its 510(k) MDUFA decisions within 90 FDA Days. In fiscal year 2013 and 2014, most branches were reaching decisions within 90 FDA days 90 percent of the time or better.

Substantially Equivalent (SE) Determinations and Pending Submissions: Improvements to the 510(k) program have increased the number of submissions determined to be substantially equivalent (SE) since 2011 (decision cohort). The number of submissions determined to be SE in fiscal year 2014 is 10 percent greater than in fiscal year 2010. The impact of CDRH improvements is further observed in the number of pending 510(k) submissions, which has been reduced by 30 percent from its highest level in fiscal year 2010.



**Excludes final decisions made on FY 2013 - FY 2015 receipts that were not accepted for review as of December 31, 2014

Chart 4. Percent of 510(k) determined to be Substantially Equivalent (SE). Percentages may not add to 100 percent due to rounding. FY 2015 includes only 3 months of data.



**Excludes FY 2013 - FY 2015 receipts that were not accepted for review as of end of year.

Chart 5. 510(k) submissions pending at end of the year. Includes 510(k) submissions under review or on hold. FY 2015 is as of December 31, 2014.

510(k) Refuse to Accept (RTA) Program: Under the RTA Program FDA conducts an early review against specific acceptance criteria to assess whether the submission meets a minimum threshold of acceptability and should be accepted for substantive review. The assessment of the completeness of the 510(k) occurs during the early acceptance review, while the assessment of the quality of the submitted information occurs during the substantive review. Since the initiation of the Refuse to Accept (RTA) program on January 1, 2013, the RTA rate has been decreasing from 58 percent during the second quarter of fiscal year 2013 to 39 percent during the last quarter of fiscal year 2014. (Chart 6)

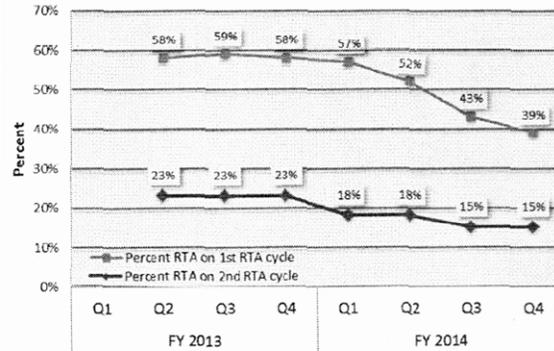
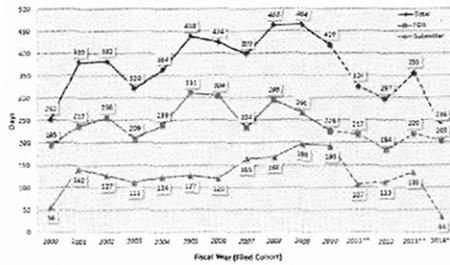


Chart 6. 510(k) Refuse to Accept (RTA) rate for first and second RTA cycles.

Training and increased FDA and Industry experience regarding the RTA process have contributed to the decreased rate while improving the quality of 510(k) submissions. FDA is undertaking a process improvement exercise to further reduce the RTA rate and improve consistency of this program. Overall acceptance rate, when RTA 1st and 2d cycles are combined, was 84 percent in fiscal year 2013 and 90 percent in fiscal year 2014.

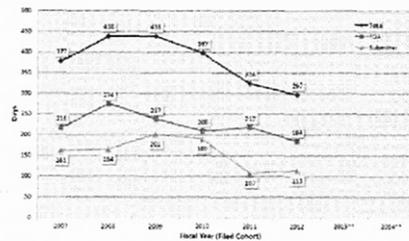
PREMARKET APPROVAL APPLICATION (PMA) PROGRAM

Average Time to Decision for PMAs: Average time to decision has decreased since its highest point in fiscal year 2009. (Chart 7) As of December 31, 2014, the fiscal year 2012 original PMA cohort was 98 percent closed, the fiscal year 2013 cohort was 72 percent closed and the fiscal year 2014 cohort was 41 percent closed. Comparison of receipt cohorts at the same closure levels show a 32 percent decrease in total review times (Chart 8) between fiscal year 2009 and fiscal year 2012 when the cohort is 98 percent closed, 3 percent decrease in total review times between fiscal year 2009 and fiscal year 2013 (Chart 9) when the cohort is 72 percent closed, and a 26 percent decrease in total review times between fiscal year 2009 and fiscal year 2014 (Chart 10) when the cohort is 41 percent closed. Examination of the applications included in these cohorts, detected a correlation between average total time to decision and panel meetings (see further explanation below).



**Cohorts are still open, average times will increase.

Chart 7. Average time to MDUFA decision for PMAs, as of December 31, 2014. Includes original PMAs only; FY 2013-FY 2014 are receipt cohorts including PMAs filed as of December 31, 2014, prior cohorts are filed cohorts; times may not add to total due to rounding. Percent of cohort with MDUFA decision: FY 2011 = 98% (42/43); FY 2013 = 72% (21/29); FY 2014 = 41% (11/27).



** FY 2013 and FY 2014 cohorts are not yet 98% closed (as of December 31, 2014).

Chart 8. Average time to MDUFA decision for PMAs. Comparison of filed cohorts when approximately 98 percent closed. Includes original PMAs only; times may not add to total due to rounding. Proportion of cohort closed (MDUFA decision) in this comparison: FY 2007 = 34/35; FY 2008 = 29/30; FY 2009 = 31/32; FY 2010 = 42/43; FY 2011 = 42/43; FY 2012 = 24/24.

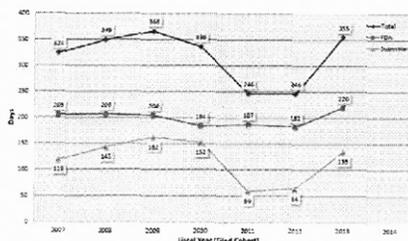


Chart 9. Average time to MDUFA decision for PMAs.

Comparison of filed cohorts when approximately 72 percent closed. Includes original PMAs only; times may not add to total due to rounding. Proportion of cohort closed (MDUFA decision) in this comparison: FY 2007 = 25/35; FY 2008 = 22/30; FY 2009 = 23/32; FY 2010 = 31/43; FY 2011 = 31/43; FY 2012 = 17/24; FY 2013 = 21/29. As of December 31, 2014, FY 2014 cohort not yet 72% closed.

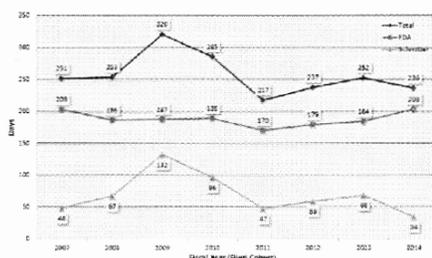


Chart 10. Average time to MDUFA decision for PMAs.

Comparison of filed cohorts when approximately 41 percent closed. Includes original PMAs only; times may not add to total due to rounding. Proportion of cohort closed (MDUFA decision) in this comparison: FY 2007 = 14/35; FY 2008 = 12/30; FY 2009 = 13/32; FY 2010 = 18/43; FY 2011 = 18/43; FY 2012 = 10/24; FY 2013 = 12/29; FY 2014 = 11/27. FY 2011 = 98% (42/43); FY 2013 = 72% (21/29); FY 2014 = 41% (11/27)

FDA is also closing the gap between the divisions with the fastest and slowest review times. Performance has decreased significantly, from a difference in total average days to final decision between the highest and lowest performing divisions of 633 days in fiscal year 2008 to 197 days in fiscal year 2014.

Effect of an Advisory Panel Meeting on Average Total time to Decision: As part of the review process, FDA may present a PMA to an expert advisory panel for its recommendations. Medical device advisory committees provide independent, professional expertise and technical assistance on the development, safety and effectiveness, and regulation of medical devices. PMAs that undergo an advisory panel review have different performance goals than PMAs that do not go to an advisory panel because holding an advisory panel meeting adds more time to a review. Examination of the fiscal year 2013 cohort shows the highest percentage of PMAs undergoing an advisory panel review since 2007, which led to what appears to be an increase in review times. But when “apples-to-apples” comparisons are made, total review times continue to show a decrease.

PMAs that undergo an advisory panel review typically take longer to reach a final decision, as accounted for in MDUFA III performance goals. Because the average total time includes both PMAs that go and do not go to an advisory panel meeting,

the spike in review time for fiscal year 2013 reflects the significantly higher percentage of applications with an advisory panel meeting (33 percent). (Chart 11) However, when comparing reviews times of PMAs with a panel meeting (Chart 12) across different years and PMAs without panel meetings across different years, we continued to see improved performance in fiscal year 2013 for both categories of PMAs. In addition, the percent of PMAs that will undergo advisory panel review in fiscal year 2014 is considerably less than fiscal year 2013. A decrease in the percent of PMAs which will go to an advisory panel meeting in fiscal year 2014 along with other program improvements lead us to expect lower average total review times in fiscal year 2014.

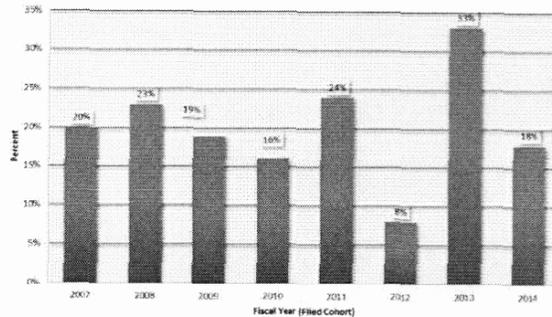


Chart 11. Percentage of PMAs with panel review, as of December 31, 2014, based on PMAs with a MDUFA decision

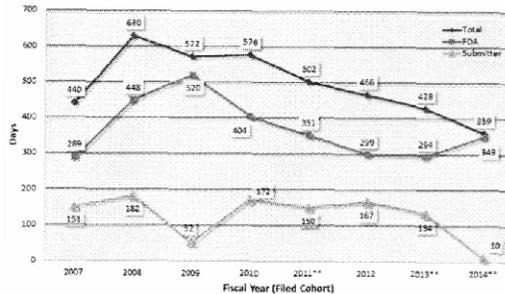


Chart 12. Average time to MDUFA decision for PMAs with Panel Review, as of December 31, 2014. Includes original PMAs only; FY13-FY14 are receipt cohorts including PMAs filed as of December 31, 2014, PMAs for prior cohorts are filed cohorts; times may not add to total due to rounding. Cohort still open, average times will increase; percent of cohort with MDUFA decision: FY11 = 91% (10/11); FY13 = 70% (7/10); FY14 = 67% (2/3)

Approved and Pending PMAs: Improvements to the PMA program have resulted in an increase in the number of applications approved since 2011 (decision cohort). The number of applications approved in fiscal year 2014 was 27 percent greater than fiscal year 2010. (Chart 13)

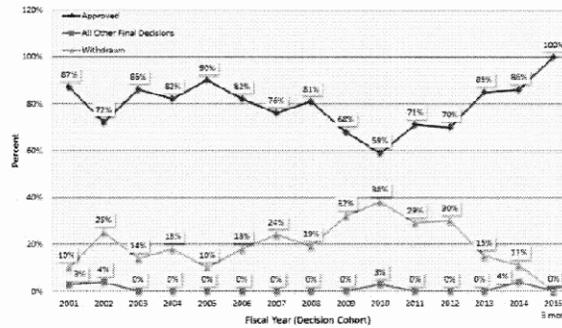
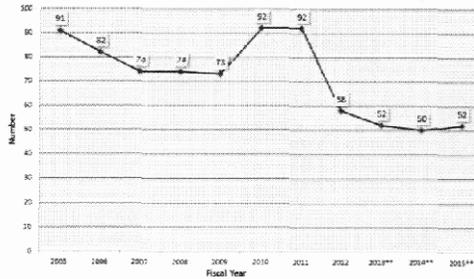


Chart 13. Percentage of PMAs approved. Based on original PMAs that were accepted for filing as of December 31, 2014; percentages may not add to 100 percent due to rounding.

Note that the fiscal year 2015 cohort only includes 3 months of data. The impact of CDRH improvements is further observed in the number of pending original PMAs, which has been reduced by 43 percent from its highest level in fiscal year 2010. (**Chart 14**)



**Excludes FY 2013 - FY 2015 receipts not accepted for review at year's end.

Chart 14. PMAs pending at the end of the fiscal year. Includes original PMAs under review or on hold. FY 2015 is as of December, 31, 2014.

DE NOVO PROGRAM

Average Time to De Novo Granting: Improvements to the *de novo* program have resulted in a 70 percent reduction in the average total time to decision for these submissions. Average total time to final *de novo* decision for devices with post-NSE *de novo* requests (includes FDA and Industry days for 510(k) NSE review and post-NSE *de novo* review) has been reduced from 992 days in fiscal year 2010 to 300 days in fiscal year 2014. Average total time to decision for direct *de novo* requests are even lower than for *de novo* requests using the post-NSE review pathway. (**Chart 15**) While time to decision has significantly decreased since fiscal year 2010, the number of *de novo* requests received has almost doubled (25 *de novo* re-

quests in fiscal year 2010 versus 46 and 41 in fiscal year 2013 and 2014, respectively).

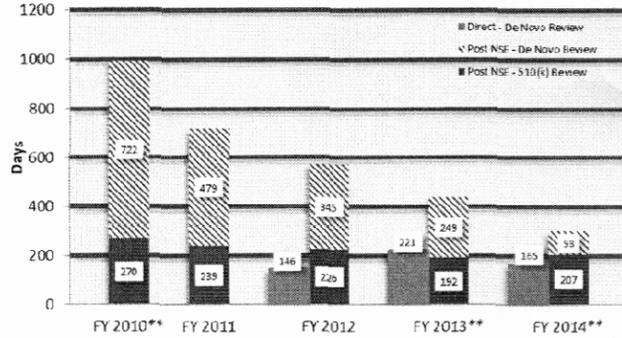


Chart 15. Average total time to final *de novo* decision for devices with post-NSE *de novo* request and devices with direct *de novo* request.

INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROGRAM

IDEs Approved within Two Cycles: Improvements to the IDE Program (e.g., establishing a formal Clinical Trials Program, process improvements, policy changes, extensive training for CDRH review staff and the device industry, and new guidance documents) have greatly shortened the time for an IDE to reach approval, so that a clinical trial can begin. The number of IDE studies that get fully approved within two cycles has increased significantly. The percentage of fully approved IDE studies within one cycle has increased ninefold compared to fiscal year 2011 and the percentage fully approved within two cycles has increased fourfold compared to fiscal year 2011. (**Chart 16**) In fiscal year 2014, 63 percent of IDEs submitted were approved within 2 cycles.

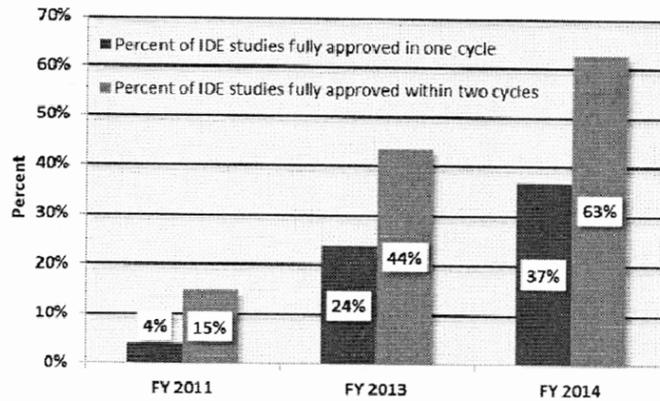


Chart 16. Percentage of IDE studies fully approved within one and two cycles.

Median Days to IDE Full Approval: The median number days to full IDE approval has decreased from 442 in fiscal year 2011 to only 101 in fiscal year 2014, reducing the time it takes to bring a new medical device to market by nearly a full year. (Chart 17)

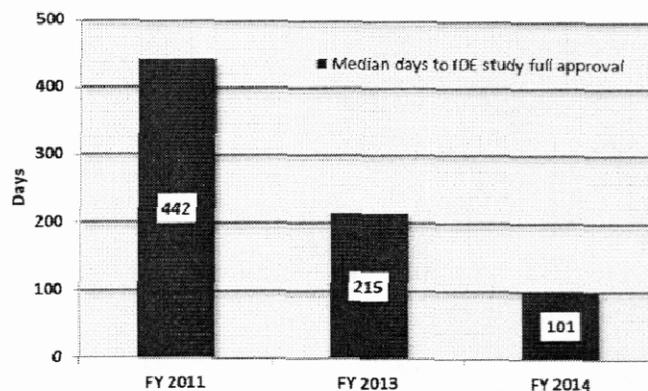


Chart 17. Median number of days to full IDE approval.

Clinical Studies: Devices that are studied in the United States in the early stages of development are more likely to reach U.S. patients sooner in pivotal studies and as marketed devices. In the past 5 fiscal years, 82 FDA approved original PMAs were supported by a single pivotal IDE study. Of those, 32 (39 percent) included studies enrolling subjects outside the United States. For *in vitro* diagnostic devices (IVD), where clinical studies are typically conducted in at least three sites, sponsors generally choose to have one of those sites inside the United States to address differences between the United States and other countries in how medicine is practiced, patient populations, and disease progression.

FDA is facilitating and encouraging the use of innovative clinical trial designs and statistical methods such as adaptive clinical trials and Bayesian statistics. For the period from 2007 to May 2013, FDA received 250 submissions that were adaptive, most of which were pre-submissions and IDEs. About 30 percent of these used Bayesian methodologies. In addition, there were 17 PMAs and PMA Supplements that used adaptive clinical trials from 2007 to May 2013, eight of which used Bayesian methodologies.

CUSTOMER SATISFACTION

Industry Customer Service Rating for Premarket Program: Excellent customer service means understanding and addressing, as appropriate, stakeholders' and colleagues' needs through active listening, problem solving, seeking out the ideas of others, explaining the rationale for our decisions and requests for information, learning from our mistakes, and doing our best. Providing excellent customer service improves our interactions supports better regulatory outcomes, thereby improving patient health.

By providing excellent customer service, we do not alter our regulatory obligations. Customer service does not mean letting unsafe or ineffective devices on the market—rather it involves identifying and meeting our customers' needs, as appropriate, while achieving our mission and vision.

The experience of receiving excellent customer service can encourage device makers to choose the United States first when bringing their products to market; in turn, U.S. health care providers gain access to the technologies that they need to administer quality health care to patients. In June 2014 CDRH began measuring customer satisfaction and established a goal of 70 percent satisfaction by the end of 2014. The Center's performance was 83 percent (95 percent confidence level and 2 percent margin of error). The performance of the premarket program was 86 percent satisfaction (95 percent confidence level and 3 percent margin of error). Among

its industry stakeholders—industry, industry consultants, and industry trade associations—was even higher, 89 percent (95 percent confidence level and 4 percent margin of error). (Chart 18)



Chart 18. Premarket program 2014 customer satisfaction rating.
The satisfaction score includes respondents who indicated they have interacted with CDRH's premarket offices.

The CHAIRMAN. Thank you very much.
Senator Roberts has an important engagement in a few minutes. I'm going to call on him at this time.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Mr. Chairman, I thank you, and I apologize to my colleagues. I have several questions I'd like to submit for the record.

I just want to say that I share Senator Murray's concern with regard to the fact that with the FDA, as the agency has grown with large new requirements to publish regulations for food, tobacco, other things, we have seen additional delays in getting guidances and regulations necessary for medical product innovation and the public health finalized and approved. I know they'll have good answers as to how they are prioritizing their work with these new authorities.

I also want to note that in Kansas, we've seen the medical research and development field expand greatly in recent years, anchored by a research hospital and medical school at the University of Kansas, the home of the ever-fighting and optimistic Jayhawks. The recent National Cancer Institute designation for KU has created nearly \$1 billion in economic activity and over 1,800 jobs locally. I am very confident we will continue to lead in this area.

I thank the chairman for his indulgence and the patience of my colleagues. Thank you.

The CHAIRMAN. Thank you, Senator Roberts, for your succinct statement.

We'll now move to 5 minutes of questions for committee members, and I'll begin.

Dr. Woodcock, you said something very important about the mandates from 2007. We know in this committee that—I mean, we are a feast of well-intentioned good ideas here, and they come from all directions, from the right and the left. We see that in higher education, where a number of us have invited the higher education

community to talk to us about simplifying regulations, and they came back with 59 specific recommendations.

Our purpose here is to enable you, not to slow you down. We want to align Federal policies—and that means our laws and our regulations—with an opportunity for more, not less, safe innovation.

I would invite each of you to form your own internal red team for red tape, and if you see things that are in the law or in regulation or even that the Office of Management and Budget makes you do that you think are nonproductive, let us know, because this train is going to get to the station. We're working with the House and the President, and this is an opportunity to clear the clutter out of the way and to take advantage of a rapidly changing landscape.

Now, Dr. Austin, we've heard a lot about the valley of death. I had some Vanderbilt researchers explaining that to me the other day. More money obviously would help. You talked about it some. What else can we do to shorten the period from discovery to medicine cabinet and this middle ground where so many—8 out of 10—medicines fail for business reasons or for medical reasons? Is there anything else we should do?

Dr. AUSTIN. Thank you for the question. First, it is important to say that there—as it will not surprise you to learn—are many, many more of those valley of death crossing projects that we have proposed to us than we can possibly fund. The number is currently 96 percent that we cannot fund.

It's important to realize that—to see change that's happened since I was in training 30 years ago, there were tens of opportunities to intervene in a rapid way for patients with untreatable diseases. Now that's in the thousands. The opportunities have really exploded.

The CHAIRMAN. If 8 out of 10 don't succeed, if that's anywhere close to right, are there any other steps you can take to reduce that number with whatever dollars you have?

Dr. AUSTIN. Yes, and to give you some examples, one beyond the direct support is that these projects traditionally have been done in a rather disparate fashion. This requires a team to do this. It requires people of different expertises, often 8 or 10 different expertises, and different sectors, so academia, biotech, pharma, VC, patient groups, regulators, and, traditionally, they've tended to work in silos.

It is one of the reasons why everything NCATS does is done as a collaboration. What we find is what our mothers told us, that many hands make light work, and if you put together a team—

The CHAIRMAN. Collaboration is one answer. Anything else?

Dr. AUSTIN. I can't let this go by without mentioning the—

The CHAIRMAN. If you can do it in 25 seconds, I would appreciate it so I can go to another question.

Dr. AUSTIN. The administrative limitations that Dr. Collins has talked about, the travel, the hiring issues. Those are big issues for us because of the—

The CHAIRMAN. I have encouraged Dr. Collins literally—I had a good visit with him last week—to form a red team for red tape and

give us a list. We know that some of those things are your fault, and some of them are our fault.

Dr. AUSTIN. Yes.

The CHAIRMAN. Some of them is the Office of Management and Budget. We can put the spotlight on all of them, and we'll try to change the ones that we can that get in the way of your good work.

Dr. Woodcock and Dr. Shuren, I have just a few seconds left. We hear that in Europe, it's easier for regulators to take advantage of outside expertise. As the world changes and so much is going on in the area in which you work, surely you can't have enough smart people inside the system to make all the decisions you need to know. Are there things we can do to make it easier for you to appropriately involve experts from outside your agencies to help you deal with these issues?

Dr. SHUREN. Well, in trying to address that, we set up what we call a network of experts. We are leveraging the networks already existing in healthcare professional and scientific organizations. I'd say our biggest holdup is some questions rely on confidential information that's in the possession of the company and it's theirs to own. And because we can't share that information, we can't leverage those experts as well as we could. That is a limitation.

The CHAIRMAN. Thank you very much.

Senator Murray.

Senator MURRAY. I want to start by mentioning two letters that I sent to the FDA about the serious outbreak in my State linked to the use of special medical scopes. I acknowledge that after my first letter, FDA took several actions to help protect patients.

Dr. Shuren, I know your center's staff is working to provide me with information about the agency's full review of this situation, a review Commissioner Hamburg committed to me in March. I want to underscore again today how important that review is so that we can work to prevent outbreaks like that from happening ever again.

Dr. SHUREN. We take it very seriously, too, and we'll be getting back to you shortly. We're also continuing to look for ways to provide more information out to the public as we continue to work with the companies, with the healthcare professionals, with hospitals, with the CDC and others. Next up, just to flag for everyone, there will be an advisory committee meeting on May 14 and 15 to discuss many of these important scientific issues.

Senator MURRAY. Very good. Thank you very much for that.

Dr. Woodcock, we've heard testimony about the extraordinary time and expense it takes to develop a new lifesaving drug, from having an idea to FDA approving a product for patients. We've heard many ideas about why this is the case and how to improve things, like better drug development tools like biomarkers.

How do you think we can cut down on the cost and time it takes to develop new lifesaving products?

Dr. WOODCOCK. The limitations, as I said in my oral testimony, are really related primarily to the science. We have been working for quite some time on improving the infrastructure that is used to move these products along and to evaluate them. I do think what NCATS is doing is extremely important, because they're doing a focused scientific effort.

It's developing new biomarkers, in which we're engaged with many consortia on; developing clinical trial networks so that each clinical trial isn't set up separately at great expense and time and then taken down, and 8 out of 10 times, nothing comes of it because the drug fails. Also streamlining electronically how we collect data from clinical trials and elsewhere, and we're making tremendous advances on that and the standards.

Now, what NCATS is doing and other people are working on is the predictive toxicology, because I believe what Senator Alexander was referring to in a great sense—this valley of death—relates to the academic community who have wonderful ideas, but they don't have the funding to advance their ideas beyond the laboratory stage and into people, because you have to do the safety testing. You can't just put laboratory chemicals into people. You have to evaluate them.

We need a more streamlined way, a common way, perhaps, that these could be evaluated and get into early clinical testing and how to get the expense down on that, or to fund it in some way, or provide more funding. As Dr. Austin said, there is very little funding that can be provided by NCATS to help all these scientists around the country take their ideas beyond the laboratory stage.

I think there are quite a number of things that can be done, but I wouldn't underestimate the difficulty of doing each one of them. They are scientific problems, and they need collective solutions.

Senator MURRAY. Thank you.

Dr. Shuren, in order for FDA to operate with speed and efficiency needed to review new products and protect public health, FDA must be staffed by some of the top scientists in the United States. Commissioner Hamburg talked to us about the challenges the agency faces in hiring and retaining qualified personnel to support your mission. Can you tell us whether you've encountered similar challenges?

Dr. SHUREN. All the time. I have great staff, but we have a very hard time recruiting and particularly retaining people. It's because, for one, I can't pay a competitive salary to industry. I can't attract people or—I train people. We are the training ground for industry. I train them. They become more marketable, and they leave and they get salaries of two or more times what they're getting paid today.

The other is if you come from industry, a lot of times your retirement is in stock just for that company. I can't wall them off. They have to divest that stock, and as a result, I've had great people say, "I'd come, but I can't because this is my family's future."

We have a high workload. This is something we deal with through user fees. But, if you combine the high workload with the less pay, then it is hard to get people, and that's why I always have a high staff turnover. As a result, it hurts companies. In the middle of a review, your lead reviewer or your medical officer leaves, and I don't have a deep bench in my center. It's a small center.

Senator MURRAY. Industry steals your employees but they need you.

Dr. SHUREN. That's exactly right, and we've got to change that, because it best serves not just industry, but it ultimately serves patients, and that's what this is all about.

Senator MURRAY. Dr. Woodcock, I assume you see the same thing?

Dr. WOODCOCK. Absolutely. I mean, our scientists need to go toe to toe with the best industry scientists, and yet when my people leave, for either academia or industry, they typically may double their salaries from what they're getting at CDER.

Senator MURRAY. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray.

Senator Scott.

STATEMENT OF SENATOR SCOTT

Senator SCOTT. Thank you, Mr. Chairman.

Thank you to the panel for participating in this hearing, and, certainly, your task is a daunting task without any question. We look forward to being as helpful as we can.

Over the last year, I had an opportunity to meet an incredibly young health advocate from Summerville, SC, a guy named Zion Thomas, who is often referred to by his nickname, The Mayor. He is an 11-year-old kid who has more energy and more charisma than most of us sitting around the table, except for his doctor and Elizabeth over there, of course. No offense, of course, to Senator Alexander.

[Laughter.]

The challenge when you start calling names is that you find yourself in trouble and digging a deep hole with a shovel that you won't put down. Anyway, I will tell you that Zion continues to be one of the strongest advocates for health issues because he, from the age of 6 months, has been in and out of the hospital because of the impact of sickle cell on his life and on his family's, and all its challenges.

I'm happy to report that South Carolina has done a pretty good job, and, specifically, the Medical University of South Carolina, which has opened a sickle cell treatment clinic that has been a breath of fresh air for Zion and his entire family. Despite the fact that sickle cell disease impacts close to 100,000 people in the United States, there is still no cure, and only one drug has been approved by the FDA to treat the symptoms of the disease.

The problem I see is that I know that companies are working very hard to find that cure for kids like Zion but, unfortunately, they continue to hit road blocks along the way. Part of the road blocks has been the approval process, according to some of the companies, with the FDA.

The main frustration I hear—and not simply from those companies trying to develop cures for sickle cell, but just companies going through the approval process—is that the agency can't quite articulate to the drug companies exactly what they are looking for from the clinical trials process in order to advance the drugs toward final approval.

Dr. Woodcock, what is the FDA doing now to ensure that companies understand through communication between the FDA and those companies what is necessary and what the results should be along the way in multiple trials?

Dr. WOODCOCK. We have negotiated under the PDUFA program something called a special protocol assessment. We have 90 days,

I think it is, or maybe less, to get back to the company. If they have a list of questions they've submitted to us—Do you agree with this trial? Will this trial be sufficient to support approval? Do you agree with these endpoints? Do you agree with these inclusion criteria, et cetera, et cetera?—we get back to them in writing, whether we agree or not. And if we don't agree, we negotiate with them until we get an agreement.

We've done over 1,000 of these special protocol assessments. This is a very valuable tool under the user fee program for the companies to get predictability about what the FDA would like them to do in order to get onto the market.

I think as a result of that and our program of meeting with companies during the development process, we have a very high what's called first cycle approval rate. In other words, when the companies submit an application to us, almost 80 percent of the time, we're able to approve it. If it's going to be approved, we're able to approve it, during that cycle, because they know what they're supposed to send us, and they're able to fulfill our requirements.

I agree with you, especially for the smaller companies, that they still feel uncertain and they want that clarity. That process is available to all.

Senator SCOTT. Thank you.

The CHAIRMAN. Thank you, Senator Scott.

We have Senator Warren, Senator Cassidy, and Senator Bennet. Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman.

This committee is beginning to develop legislation to accelerate the development of new cures and treatments. To do that effectively, we must start with where medical innovation comes from. Real innovation comes from NIH. A recent analysis by Harvard researchers found that most of our truly transformative drugs are based on insights gained through federally funded research.

Another analysis found that two-thirds of the 21 highest impact drugs approved between 1965 and 1992 stem directly from public sector research. The private sector commercializes these discoveries, but they would never happen in the first place without strong government support.

Now, the industry knows this. The Biotechnology Industry Organization testified that, "There is no private sector alternative for much of the basic research that NIH supports." John Castellani, President and CEO of PhRMA, has said that,

"Government-supported basic research is one key to how we collectively progress in discovering novel compounds for addressing patients' unmet medical needs."

Dr. Austin, do you agree that many of the drugs on the market today are based on scientific insights gained through NIH or other publicly funded research?

Dr. AUSTIN. Absolutely. It's a fact.

Senator WARREN. It's a fact. Good. We'll go with that.

Dr. Pettigrew, in addition to providing the basic science used to develop new drugs, can you describe other ways that we benefit from NIH-funded research?

Dr. PETTIGREW. Thank you for the question, Senator. I think the issue here really is impact, as you pointed out. This is a process that is a continuum. It starts with basic science. The objective of basic science is to understand the laws of nature, and with that understanding, we are more informed about how things work and what goes wrong. That leads to fashioning solutions to these problems, and then those solutions have to be translated.

The other things that we do at the NIH is to integrate that knowledge with our ability to invoke the practical solutions and design them through engineering and the physical sciences along with the life sciences to fashion such solutions to the kinds of problems you identified.

Senator WARREN. Dr. Austin, would you like to add anything to that?

Dr. AUSTIN. A couple of things. The first is that—and I can speak from both sides of this, because I'm a basic researcher by training, but I'm also a clinician, and I also spent many years in the pharmaceutical industry. I've seen all sides of it.

Fundamental science is the seed corn on which all interventions are based. It is necessary, but almost never sufficient. This is a very long process of going from—what fundamental science does is fundamentally to figure out how something works normally, and when it breaks, why does it break.

Then the issue is how to fix it, and how to fix it actually requires a quite different skill set in any field, from figuring out why it's broken, and translation is really to fix it, and that's a completely different field. Sometimes there's a feeling that the intervention to improve what's broken happens kind of naturally, and it's well worked out about how to do this, and we know how to do it.

The fact is, as Dr. Woodcock was saying, our understanding of this process is extremely poor. The science underlying the translational process is extremely poor, and our operational structures to do it are extremely poor. So I would say, yes, basic science is the seed corn of everything, but it requires enormous energy to get through the next 10 or 15 years to actually have an intervention which improves human health. That's what we're working on.

Senator WARREN. Dr. Woodcock, I see you nodding yes. Would you like to add an amen to that?

Dr. WOODCOCK. Well, I think Dr. Austin put it extremely well. It's very under-appreciated, and I'm sure you all have researchers coming to you—because I do all the time—saying, "I discovered this. It should be treating people tomorrow." All right? Actually, then, when you think it takes 15 years to get from a discovery to actually treatment, people really don't understand what goes in between there.

There's an enormous amount of work and effort, and, frankly, at that stage, at the "I have a discovery" stage, it's 10,000 compounds getting down to one that actually gets approved. And that isn't because of FDA requirements. That's because of the scientific process.

Senator WARREN. Let's just stay focused on that about the scientific process, then, if we're talking about innovation. We have to

be blunt. Medical research funding in this country is in crisis. Since 2003, the NIH budget has not even kept pace with inflation. Its purchasing power is down about 25 percent. To increase medical innovation, the NIH needs more resources. We've got to keep this pipeline going.

Last week in the *New York Times*, Newt Gingrich said that when it comes to breakthroughs that could cure—not just treat, but cure—the most expensive diseases, government is unique. It alone can bring the necessary resources to bear, and it is ultimately on the hook for the cost of illness. It is irresponsible and short-sighted, not prudent, to let financing for basic research dwindle.

I agree. If we want medical innovation in this country, we need to double down on support for NIH. If we want to improve the quality of life for Americans and reduce Federal healthcare spending, we need to double down on NIH spending.

This committee has a chance to make a real difference, Mr. Chairman, but that chance begins with support for the NIH. Thank you.

The CHAIRMAN. Thank you, Senator Warren.
Senator Cassidy

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. Dr. Woodcock, I asked Dr. Hamburg just before she left, but I wasn't really quite sure I could comprehend the answer. The Manhattan Institute did an FDA report card finding wide variance in performance among the agency's drug review divisions. For example, median drug approval in the fastest division, oncology, was two to three times faster than neurology, cardiovascular, and renal. Neurology took nearly 600 days to approve a new drug. Cardiovascular took 400. Oncology and antiviral took slightly less than 200. These high performers, oncology and antiviral, actually have a higher workload than the other divisions.

Now, I've learned in life that leadership often plays a role. Given the problems that you and Dr. Shuren—presumably, those are common in both. What metrics do we have on these divisions? How do we explain the difference? How do we minimize it?

Dr. WOODCOCK. Well, I think that report was highly misleading. First of all, CDER met all PDUFA goals. They have six timelines for getting back to companies with a full review, and all those divisions met their timelines. I can tell you, though, if the Nation had declared a war on neurodegenerative disease at the same time they declared a war on cancer, we wouldn't be having this conversation.

Senator CASSIDY. Now, let me ask—and I agree with you. We need a war on neurodegenerative disease. Believe me. I'm with you. That said, it does suggest that the workload at the antiviral and the oncologic divisions is actually higher, and yet they have approval times that are one-third of those of the others.

Dr. WOODCOCK. Yes, and they—

Senator CASSIDY. Then we have had a war on cardiovascular disease, and that's one of the divisions that does poorly.

Dr. WOODCOCK. Well, does poorly. All right. When cardiovascular disease—we have a large number of treatments available for myocardial infarction. I won't go into this in great detail, but, we have

a large number of available therapies. These are comparative trials that are done. They often involve 25,000 patients or more.

To review that level—and they often have very small incremental benefits, like 0.1 percent improvement in mortality or stroke or something like that. That’s quite a different issue than, like, what Senator Murray was talking about—breast cancer, where that drug doubled the time that it took for the tumor to start growing again.

These are apple and orange comparisons, I believe. And I will tell you that I was at the center a decade and a half ago when the oncology division was routinely criticized over and over and over again for not approving cancer drugs fast enough. Now, because of advances in genetics, we actually understand the molecular basis—

Senator CASSIDY. May I interrupt just for a second?

Dr. WOODCOCK. Yes.

Senator CASSIDY. Again, I have limited time. I don’t mean to be rude. One marker that kind of sorts things out sometimes is your turnover in each division. Obviously, if there’s more turnover—and you alluded earlier, you and Dr. Shuren—turnover can play a factor. Are the turnovers in the divisions constant? Are they all similar?

Dr. WOODCOCK. Well, I would say in the neurology division, due to the problems that Dr. Shuren was alluding to in hiring and competitiveness of our salaries, we are really down on neurologists. We’re having a desperate time getting enough neurologists, because the good news is that research in neurodegenerative diseases is actually picking up. We’ve had some turnover in that division with retirements of people who have been there a long time, and we cannot really recruit neurologists. This is a huge issue for us.

Senator CASSIDY. I got you—and not to cut you off.

Dr. Austin, I walked in from another hearing as you were speaking about these consortiums and some of the problems thereof. I’m really interested about the intellectual property rights as we go forward. I have an article from 2012, “Recalibrating Intellectual Property Rights to Enhance Translational Research Collaborations.” It makes sense to me that if you have a consortium, and you come up with an invention, someone has to figure out who owns the IP.

Dr. AUSTIN. Yes.

Senator CASSIDY. That in itself—you’ve got to use somebody else’s IP, which—I’ve learned a new term—if it’s a platform, they can choke off the research if the licensing fee is too high. I’m actually seeing people in the audience nod their heads. What thoughts do you have? Do we need to do something legislatively about this IP? Because I do get a sense that this is a choke point going forward.

Dr. AUSTIN. The good news is—I can tell you from our perspective—we have never had a project fail because of IP.

Senator CASSIDY. I was told that industry is going to be different than government. Government tends to make it work better. Industry is going to be the sticky wicket.

Dr. AUSTIN. About half of our projects are with companies, and we have—probably the reason that we have made this work is that we view this area that you’re describing as an area of innovation. Science is not the only area that needs innovation. Novel public-

private partnership models is also a model of—a way that we innovate.

If we have time, I could tell you about some of the examples that we've developed and that are——

Senator CASSIDY. I'm out of time, so let me ask you this quickly. Do we need to do something legislatively, or is this something that you all are going to be able to figure out? Because otherwise, there's going to be bipartisan agreement in addressing an IP issue that's going to thwart cost-effective relations——

Dr. AUSTIN. This is something that I'd have to consult with my NIH colleagues and get back to you with.

Senator CASSIDY. Please. If all of you would do that—I mean, you know better than we. We are willing to help you. I don't understand IP, but the Chairman is a lawyer, and he tells me he can handle it.

I yield back. Thank you.

The CHAIRMAN. That's a very helpful question, and we would appreciate a response on that.

Senator Bennet

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman, and thank you for holding this important hearing. I thank all the panelists.

Dr. Woodcock, I was hoping you could touch briefly on what we've learned through the new breakthrough therapy process that's been set up at the FDA. I want to thank you for working with us on that bill. When Peggy Hamburg was here, she testified that 23 of the 55 drugs approved during her time as Commissioner of the FDA came through the breakthrough therapy process. So something must be working.

As you know, Senators Burr, Hatch, and I also recently introduced a parallel bill on the device side, and I wonder whether you, Dr. Shuren, could also comment on the potential for that. What are the pitfalls? What are the limitations, but also the successes?

Dr. Woodcock.

Dr. WOODCOCK. Well, this program has been much more active than we expected. We expected, based on historical trends, that we would see one or two breakthrough drugs a year. We've designated, since the program was enacted, 84 drugs. Not all of them are going to make it, and I think that's the major pitfall. We don't want to raise the hopes of desperate patients, and then only to have that drug fail.

People have to be clear that when we designate a breakthrough, it doesn't mean it's going to work at the end of the day. However, we have approved 24 of these, and the track record is very good, that, usually, that early clinical indication is right.

The interesting thing about breakthrough—and I think the most important thing—is it has shortened the development time. That's really a first time. These other things have focused on FDA review. For a priority drug, FDA review is 6 months or less. There's not much to come and go on there.

We have the 15 years of drug development time, and the breakthrough designation—by FDA working very closely with the companies, we've had companies come up and testify and so forth that

up to 2 years has been cutoff of that development time. I think it's a successful program.

It is, again, stressing, where staff, to Senator Cassidy's point—many of them are antivirals and oncology drugs because the science is advanced due to HIV and the war on cancer. We understand those diseases better and we're able to actually develop better therapies. However, the good news is we've had designations in psychiatry and we've had designations in serious dermatologic conditions and rare diseases of children and so forth, and we can only hope that those bear fruit as well.

Senator BENNET. What explains—you said you thought maybe we would have one or two designated, and now we've got 80 designated and 24 approved. What explains that delta between what we thought was going to happen and what actually has happened?

Dr. WOODCOCK. I believe there's been an inflection point in drug development. You know, everyone was very upset about drug development. It was slowing down in the early 2000s and mid-2000s.

Really, what happened is the companies started investing in innovation, and it's the advances in science—what Senator Warren was talking about—that are paying off in certain fields. We know enough that we can—Chris was talking about the fixes to the problems. We know better what to target and how to do that.

For antivirals, for cancer drugs, we can actually get drugs that are highly effective. Most of the older drugs maybe only work—6 percent improvement or something like that. These breakthroughs we're seeing—we're seeing curative therapies in some cases.

Senator BENNET. Dr. Shuren, could you talk a little bit about the potential in the medical device side and what some of the things we should be thinking about are as we explore this?

Dr. SHUREN. The potential here is tremendous, and we're very excited to have a breakthrough device program at the center. We started piloting this approach back in 2001 as the Innovation Pathway. In fact, one of the products that came through had funding support from NIH, and I think that's a nice example where, for government, we might be able to marry up this investment in important technology and then move it through the regulatory process in a much more streamlined fashion, with collaboration between NIH and FDA.

While we just launched that program the other week formally, based on our experiences, I want to first of all say thank you to you and Senator Burr and Senator Hatch for the opportunity to work with you in providing some suggestions in legislation to help sort of codify and maybe move that program forward more expeditiously.

Senator BENNET. Mr. Chairman, I'm out of time or about out of time. I just want to make one observation. When I first got here 6 years ago, I used to say that it was nobody's day job in Washington to figure out how we are going to keep a thriving bioscience industry here in the United States.

I think it would only be fair to say we have made a tremendous amount of progress in the last number of years in part because of the leadership at the FDA. I'm grateful for it. I think we have a long way to go, but I think we are certainly moving in the right direction.

The CHAIRMAN. Thank you, Senator Bennet.
Senator Isakson.

STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Thank you, Chairman Alexander.

Dr. Woodcock, I was at the Association of County Commissioners convention in Georgia last Sunday. That may seem to be irrelevant to this hearing. Ross King is the association director for the county commissioners of Georgia. His daughter, Jackie King, died last year. She died of melanoma. In her 2-year fight against melanoma, she joined up with me to help promote the Sunscreen Innovation Act which we passed here about 6 months to a year ago.

My question to you is this. The surgeon general has issued a call to action on skin cancer. More Americans have skin cancer than lung cancer, prostate cancer, breast cancer, and the others combined. It costs us \$8.1 billion a year.

One of the cancers that comes directly from the sun is melanoma, which is the deadliest of all cancers. I have had two, which, fortunately, I got in time. It's a very deadly cancer. It's what Jackie King died of.

Why is it that now that we've passed the Sunscreen Innovation Act, which directed the FDA to look at these ingredients in over-the-counter drugs that are approved in foreign countries, that are innovative and helpful in sunscreen—why do you continue to delay in taking action? Some of those have been pending for 12 years.

Dr. WOODCOCK. We have taken the actions directed by the Sunscreen Innovation Act. The way the process is set up for the monographs for how over-the-counter ingredients are regulated—we have followed that process. That process calls for data submission prior to the finalization of the monograph for products. That is the scheme that is currently in effect.

Senator ISAKSON. If you carried that scheme to its conclusion, when will we have some results?

Dr. WOODCOCK. Well, it would require the manufacturers to submit the data that we have asked them to submit about the safety of these additional sunscreens to the FDA, and then we—the monograph process is a regulations process. We have to propose and finalize regulations for each segment of any monograph, and there are multiple categories.

There are 88 categories of over-the-counter drugs, I believe, that we need—to go through this process. Some of them are in final form. The sunscreen one is not.

Senator ISAKSON. The monograph is not in final form?

Dr. WOODCOCK. Right.

Senator ISAKSON. Is that because you don't have what you need from the manufacturers of the ingredients?

Dr. WOODCOCK. In part, and in part it's because the monograph process follows a sort of stately progression, and as the science evolves, the process of proposing and finalizing regulations always seems to lag behind the scientific changes that occur. We're always trying to catch up. We started on the monograph for sunscreens in the 1970s, and we're still working on it.

Senator ISAKSON. Well, it's been a long time, and it's time to bring some of it to a conclusion. I know you can't answer this off

the top of your head, but if you would, let me know or let the committee know what the progress is on the sunscreen ingredients, if there are any manufacturers who are delinquent in getting you the information that you need. Please let us know, because I would like to do everything we can to promote them getting all the information in so you can do it in a timely fashion—finish your monograph.

Dr. WOODCOCK. I totally agree, and we will be happy to get back with you.

In fact, I introduced the regulation that allows these other ingredients to be considered in the monograph process in the late 1990s so that we could put more ingredients into this process.

Senator ISAKSON. All right. I'm getting ready to show my ignorance because my staff is always smarter than I am, and I've just been handed a note, so I'm going to ask this question. If it's a dumb question, my staff got me to ask it.

[Laughter.]

And since it's my staff, I know it's not a dumb question. The bill changed the law and gave sunscreen a separate order process. Is that correct?

Dr. WOODCOCK. That's correct for the time and extent, to my understanding, but not for the final process.

Senator ISAKSON. Has that time and extent been expedited?

Dr. WOODCOCK. To the extent we were able to under the new law, we've obeyed all the provisions.

Senator ISAKSON. Because that's really what led to the whole Sunscreen Innovation Act, because one of those time and extent applications was 12 years old and still did not have action. I'm not trying to pick on you, but it's a big important—anybody that's lost a child to melanoma or anybody that's suffered from skin cancer knows how important it is.

Dr. WOODCOCK. You are not picking on me, and I share your frustration about the monograph process. It is not very functional in today's world.

Senator ISAKSON. Well, I'll pick on Dr. Shuren for 1 second.

Dr. Shuren, we sent you a letter about a year ago asking about the draft guidance. Right before the May 10th hearing, you submitted a partial list of the amount of draft guidance that FDA had issued. This Friday, we got the rest of that list to the committee, and I have it before me. It lists whether you're going to withdraw draft guidance, finalize draft guidance, or reissue draft guidance.

My question is just—and you don't really need to respond to this except to respond in writing. Will you let us know when you plan to take those actions on finalization, revision, or withdrawal? There are 144 pending draft guidances for the agency right now. We'd like to know what the timing of those is going to be.

Dr. SHUREN. I know we'll get back from the agency.

I can say for the device program, we're withdrawing 30 from last week. The 43 remaining—the 40 we will finalize within the next 18 months, and the majority of those are actually less than 5 years.

The other thing I'll point out is we put in performance goals in December of last year about finalizing draft guidances, commitments that we will finalize 80 percent within 3 years, 100 percent by 5 years, or reissue or withdraw. That's our starting point, and we hope to make greater progress from there, too.

Senator ISAKSON. Thank you very much.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Isakson.

Senator Murray, do you have any closing comments or questions?

Senator MURRAY. Well, Mr. Chairman, thank you for this hearing. I thought it was really excellent. I do have a few more questions. I will submit them for the record to get responses.

I thought this was a great hearing. We've got a lot of work in front of us, but I think, working in a bipartisan way, we can move forward, and I appreciate your work on this.

The CHAIRMAN. Thanks, Senator Murray.

Dr. Woodcock, you said the monograph process—you seemed to suggest the monograph process is outdated. Who requires it? Do we require it, or do you require it?

Dr. WOODCOCK. The monograph process was a workaround around the 62 amendments which required efficacy data for all drugs that would be on the U.S. market. It wasn't known, but there were up to 500,000 over-the-counter drugs which apparently came from about 200 active ingredients.

The CHAIRMAN. Well, let me ask this. If you were the king or the queen, would you change it?

Dr. WOODCOCK. Yes. I would have a more effective process to finalize the monographs and also keep them up to date with modern science, because at the time it was done, it was thought we could just put a monograph out, and then we'd be done. We've learned things like the toxicity of Tylenol, acetaminophen—

The CHAIRMAN. Would that require a change in the law?

Dr. WOODCOCK. It would require something.

The CHAIRMAN. Would you please give our staff technical advice about what that change might look like?

Before I conclude, I see Senator Casey is here. He was here earlier, so let me call on him now, and then we'll conclude the hearing after that.

STATEMENT OF SENATOR CASEY

Senator CASEY. Mr. Chairman, thank you. I want to thank you and the Ranking Member for the hearing. I know I've been in and out, so I'll be within my time limit for sure.

Dr. Woodcock, I wanted to start with you with a question, but I first wanted to ask you—I notice you went to Penn State? Are you a Pennsylvania native?

Dr. WOODCOCK. I am.

Senator CASEY. Where are you from?

Dr. WOODCOCK. Hollidaysburg, PA.

Senator CASEY. Blair County.

Dr. WOODCOCK. Absolutely, yes.

Senator CASEY. I just wanted to get that on the record.

Dr. WOODCOCK. Idyllic childhood.

Senator CASEY. I wanted to ask you, in the context of rare pediatric diseases—I understand that FDA recently awarded the third and final priority review voucher as authorized under FDASIA. I wanted to ask you, in particular, regarding this question. What are the three products that were approved and awarded that priority

review voucher—or vouchers, I should say, plural. I don't know if you have that.

Dr. WOODCOCK. I do have that here somewhere, because I think that is important. There was one for a tropical disease. There was—hold on. I'm sorry. We can get back to you on that. Yes, we did—here they are. Vimizim for Morquio Type A syndrome; another one called Unituxin for pediatric people with high-risk neuroblastoma; and then recently Cholbam, cholic acid for bile acid disorders and peroxisomal disorders.

Those are obviously very rare diseases where there was not very much satisfactory treatment available. That's really good news.

Senator CASEY. I appreciate that, and maybe we'll followup with some questions about companies that are interested in seeking a priority review voucher. That would be helpful, and we can submit these for the record.

I want to thank you for that. I just have a last question, I guess, for Dr. Austin regarding the so-called tissue chip.

Let me just ask a preliminary question. Is the product safe now for use in humans?

Dr. AUSTIN. No. That's an important question. This is a research project at this point. This project only started 3 years ago. It's made much more rapid headway than I anticipated, at least. It is very much in the testing-validation stage now. We are working very closely—and have from the beginning—with colleagues from the FDA about this.

Perhaps within 3, 4, or 5 years, we'll be at the point where this might be able to be used for some conditions of qualification. But, there's a lot more work to go.

At this point, the most immediate applications—and we're beginning to see this already—a number of these chips are being used actually in research applications to be able to understand human diseases and why they happen and how they might be fixed in a way that works better and more quickly than animal models. For regulatory applications, the requirements are simply much more stringent. We're definitely working in that direction and working hand-in-glove with the FDA, but we have a ways to go.

Senator CASEY. I'll leave the rest of the time. I want to thank our witnesses for being here. I also want to, Mr. Chairman, thank you and the Ranking Member, and I'll refer back to something Senator Warren said and that a number of us have been saying for a number of years. We have to get more researchers to NIH for all the reasons that were cited, and, frankly, we're years behind in doing that.

Thank you very much.

The CHAIRMAN. Thank you, Senator Casey, and thanks, Senator Warren.

Let me thank the witnesses. You have distinguished careers. You run immensely important centers and, in one case, an institute. You know the ways of Washington. I mean, if we wanted to talk about Obamacare or right-to-work laws, we could have a big fight on this committee.

Senator Murray and I aren't interested in a big fight on this subject. We're interested in getting a result, and we're not here to

make it harder for you to do your job. We're here to enable you to do it better.

We would like to know from you, specifically, what we can do to make it easier for you to align Federal policies with innovation so that we can get discoveries and treatments all the way through the process into the medicine cabinets so they can help Americans. We know that part of that has to do with funding, and we'll discuss that, and we'll deal with that in the Appropriations Committee and to some extent here.

There are bound to be other specific things that, with your experience, you sit there some days and say, "Why do I have to do this when I could do it better?" For example, if the monograph is outdated, and if there's a way to fix it, we'd like to know how to fix it.

If it makes a difference at NIH, as Dr. Collins says it does, to give you a chance to take the funding that we appropriate for 1 year and roll it over to the next year, as we do with some agencies, then please put that on your list. In other words, we would like to invite you to give the bipartisan working group that Senator Murray and I have formed specific suggestions from your agencies about what we can do to enable you to do your job.

We don't want to produce a bill that reduces your productivity. We'd like to increase it. You know what you're doing much better than we know what we're doing. We'll still be appropriately critical. We'll have our questions. We're here to enable you, and we invite that.

The time for receiving that is the next few months, because right now, we're working on elementary and secondary education. We're doing pretty well with that. We're going to move next, as a major priority, to the Higher Education Act, and in the meantime, we're getting ready for this. As I said earlier, we're working on a parallel track with the House. We're working with President Obama, who is very interested in the precision medicine initiative, as all of you know.

This is an invitation that I hope you won't pass up. We thank you for your service, and we look forward to your further comments.

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. The next HELP Committee health hearing will be on May 5th. The committee will stand adjourned. [Whereupon, at 11:27 a.m., the hearing was adjourned.]