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CONTINUING AMERICA'S LEADERSHIP: ADVANCING RESEARCH AND DEVELOPMENT FOR PATIENTS

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING CONTINUING AMERICA'S LEADERSHIP, FOCUSING ON ADVANCING RESEARCH AND DEVELOPMENT FOR PATIENTS

MARCH 24, 2015

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CONTINUING AMERICA'S LEADERSHIP: ADVANCING RESEARCH AND DEVELOPMENT FOR PATIENTS

TUESDAY, MARCH 24, 2015

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

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

Present: Senators Alexander, Murray, Burr, Collins, Hatch, Cassidy, Mikulski, Casey, Franken, 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: Advancing Research and Development for Patients. Ranking Member Senator Murray and I will each have an opening statement, and then we'll introduce our panel of witnesses. After our witnesses' testimony, Senators will each have 5 minutes of questioning.

We welcome Senator Cassidy and Senator Warren to their usual positions and Senator Franken and Senator Mikulski and Senator Bennet. A lot of people are here today.

This is the second hearing on a major initiative of this committee: our effort to examine how we get drugs, devices, and treatments from the discovery process through the regulatory process into the medicine cabinets and doctors' offices.

I'd like to begin today by telling a story that illustrates why we're doing this and why it's important to get a result. Just last week, Ginger Birnbaum from Chattanooga visited my office and told me about her 3-year-old son, King. King has cystic fibrosis, and today there is no medicine to treat his form of the disease.

King's family must simply treat his symptoms. His older sister, Virginia, who is 6, helps set up his feeding tube at night since the disease doesn't allow him to digest and absorb the nutrients he needs. She walks with her friends to help raise money, to try to raise funds for research. They left me with their Christmas card with the children on it.

There is good news for some cystic fibrosis patients. We heard about it when the President announced his Precision Medicine Initiative at the White House. There is a drug that can actually treat

the underlying cause of cystic fibrosis in just about 9 percent of cases.

This drug, the first personalized drug for cystic fibrosis, was approved in 2012, 3 months after the developer of the drug submitted to the FDA a new drug application. That's the good news. The bad news is that it took 15 years from discovery to the FDA's door. It also took another 3 years from that approval in 2012 to approve the same drug for children 2 to 5 years old.

The same company is currently studying other therapies for different forms of cystic fibrosis. If all goes well, King, the child I was talking about, could have a drug that treats his form of cystic fibrosis soon.

My question is: What can we do here in Congress to help shorten that process? Or, if that drug is not successful, what can we do to shorten the discovery and development process so that King doesn't have to wait another 15 to 18 years for the next personalized medicine?

Earlier this month, we heard from Dr. Collins, the head of NIH, and Dr. Hamburg, the Food and Drug Administration Commissioner. They provided insights into what NIH and FDA have been doing to try to improve the discovery, research and development, and regulatory processes from the government perspective.

Today, our goal is to hear from the researchers and the innovators that interact with the NIH and FDA and can tell us, in their opinion, how this is working and what are potential solutions.

I've found the best ideas often come from outside of Washington. The witnesses today are from outside of Washington. Senator Murray and I have agreed on them. We call this a bipartisan hearing for that reason, and it represents much of the biomedical research and development system.

We'll hear from the academic who makes the discovery, from the venture capital community who funds further development, and from a company who takes discoveries through the regulatory process and makes them for patients. We'll also hear from a group that has been studying how to improve the discovery and development process, from improving clinical trial efficiency to creating a more predictable FDA. We plan to hear from patients and their families, like King, throughout this process as well.

I'm looking forward to hearing today about how to decrease red tape and administrative burden. We'll hear about exciting new technologies. One of our goals is to make sure that the FDA and others are ready for these technological 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 cabinets, and much of what the report covered is relevant here today. We found that medical products take more time and money to discover, develop, and reach American patients than ever before.

We also found that FDA has struggled to regulate 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 reported that the venture capital community is shifting investments away from early stage drugs and devices as a result of

increasing regulatory burden and uncertainty. We also found that countries across the globe have sought to capitalize on America's shrinking competitive advantage in the biomedical space.

These are big challenges that are slowing down the process for getting the cutting edge innovations we are discovering into the medicine cabinet and the doctor's office. The NIH and FDA must keep pace with today's cutting edge scientific advancements.

I'm looking forward to hearing your unique perspectives on these challenges and others you see as standing in the way of innovation. I am especially interested in your ideas about how to solve these problems.

Senator Murray.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Chairman.

Thank you to all of our witnesses for being here today.

As Senator Alexander mentioned, at our last hearing on advancing medical innovation, we had the opportunity to hear from NIH Director Collins and FDA Commissioner Hamburg. They talked about their agencies' roles in helping drive development and approval of treatments that save and improve lives across our country.

At that time, I laid out some principles I will be very focused on, including supporting NIH and basic investments in research, finding ways to get patients safe and effective treatments as quickly as possible, and prioritizing the needs of women and children in the product development and approval process, and above all, protecting and upholding the deep trust that families place in FDA when they reach into their medicine cabinet or take a trip to the drug store.

It's very clear in my home State of Washington and across the country that medical innovation is at a critical moment right now. Researchers and physicians are looking at prevention and treatment in a whole new way. And medical advances have changed the way we tackle devastating diseases like cancer, cystic fibrosis, and many others.

At the same time, the life sciences are helping to drive economic growth and job creation. I have seen this first hand in my home State of Washington. According to our State Department of Commerce, the life sciences sector in Washington State directly employs 34,000 individuals and indirectly employs another 57,000, and that's continuing to grow.

Thinking about ways we can continue to advance medical innovation is both good for families' health and good for our economy. The HELP committee has a strong tradition of bipartisan process in this area.

In 2012, for example, we added accelerated approval to allow the FDA to approve new drugs faster for serious conditions and unmet medical needs. We also added a breakthrough designation for promising new drugs so that researchers can find out earlier whether these treatments are effective.

These bipartisan successes have made a real difference for patients and families. While we learned from Commissioner Hamburg

just 2 weeks ago that FDA's drug approval times are the fastest in the world, we must continue to look for new efficiencies.

We all know that Congress can't legislate new cures into existence. If we could, I know we would. But what we can and must do is give our Nation's biomedical community the right tools to innovate for patients, now and for generations to come.

That means making sure that NIH is well-supported, as Director Collins urged us to do. This also means making sure that the doctors and scientists at the FDA have all the tools and resources they need so they can be engaged early in the development of new products and can help innovators get new safe and effective treatments to patients as soon as possible.

We also need to expand our use of medical data. We have a wealth of medical information that, when shared in a timely and secure way, will help us make sure the right treatments are reaching the right patients and help us better understand different groups' unique health needs, including women.

It is important we look at the entire spectrum of medical innovation, from basic research, through development and approval, and into the post-market setting.

While we, of course, want to get patients treatments as quickly as possible, speed cannot come at the expense of safety. New doesn't always mean better.

As the Institute of Medicine warned us in 2007, a regulatory culture too focused on speed can seriously damage public confidence in product safety. We need to ensure we are both encouraging innovation and upholding the highest standards of patient and consumer protection.

I'm pleased that today we will be able to hear from key players in medical innovation, from the private sector to academia, about the ways you all think we can step up to these challenges and help more patients and families get life-changing, lifesaving cures and treatments.

Thank you all for being here and sharing your expertise. I'm really confident our bipartisan work to advance medical innovation for patients will be stronger with your input. As our discussions continue, I'm looking forward to hearing from patients and advocates who can share insights into the improvements our communities want to see.

It's so important to me that the perspective of patients and their families be prioritized throughout this effort. They are the ones hoping for new cures, searching for better treatments, and looking to all of us here for solutions. I'm very hopeful that working together, we can continue the strong tradition of bipartisan success we have had in advancing medical innovation and deliver for the families we serve.

With that, I'll turn it back to you, Mr. Chairman. Thank you.

The CHAIRMAN. Thank you, Senator Murray.

I'll introduce three witnesses, and then I'll let Senator Burr introduce the first witness. The second witness is Mr. Alexis Borisy. Mr. Borisy is a partner in Third Rock Ventures, a venture capital firm based in Boston that invests in biotech startup companies. He has more than 20 years of experience building and operating innovative science-based organizations.

Our third witness, Mr. Michael Mussallem, is chairman and CEO of Edwards Lifesciences. He is considered a global leader in heart valve transplants. The medical device development process and challenges are distinct from the challenges facing drug development.

I thank you for being here to share that perspective.

Our fourth and final witness is Mr. Allan Coukell, who leads the health projects at the Pew Charitable Trust. Mr. Coukell has led many projects at Pew examining how to improve medical product development and regulatory processes.

Now I'll ask Senator Burr to introduce the first witness.

STATEMENT OF SENATOR BURR

Senator BURR. Thank you, Mr. Chairman, for the opportunity to introduce Dr. Bruce Sullenger from Duke University in North Carolina. As I often remind my colleagues on this committee, I'm proud of North Carolina's innovative biomedical research and development. It's good for North Carolina and it's good for patients across the country. I'm delighted that one of our leaders in this area is here with us today.

Dr. Sullenger, thank you for taking the time to be with us to speak to us about the great work you and your colleagues are doing at Duke, particularly your expertise about how we can accelerate and successfully commercialize promising concepts off the research bench that will reach America's patients in as timely a manner as possible.

Dr. Sullenger is a professor in the Department of Surgery and the director of Duke's Translational Research Institute at Duke University Medical Center. For almost 30 years, Dr. Sullenger has been working on the development of DNA and RNA-based translational therapies, and he is one of the pioneers in this field.

Since joining Duke in 1994, Dr. Sullenger has developed an internationally recognized translational research program and has served as the director of Duke's Translational Research Institute since 2007. In this post, Dr. Sullenger leads the university's efforts in translating scientific discoveries to uses in a clinical setting. Much of his work has been funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Dr. Sullenger received his undergraduate degree from Indiana University and completed his Ph.D. work at Cornell Medical Center and the Memorial Sloan-Kettering Center in New York. Following his Ph.D., Dr. Sullenger studied under Nobel Laureate, Dr. Thomas Cech, at the University of Colorado.

Thank you, Dr. Sullenger, for being here and probably representing the next champion of the NCAA basketball tournament yet to be finished, the Duke University Blue Devils. Welcome.

The CHAIRMAN. An appropriately parochial comment from Senator Burr. But he may be right.

[Laughter.]

Thank you, Senator Burr, and thanks to the witnesses.

If you can summarize your comments in about 5 minutes, that'll give Senators more time to have a conversation with you. Why don't we start with Dr. Sullenger—and good luck in the NCAA—and let's go right down the row.

STATEMENT OF BRUCE A. SULLENGER, Ph.D., DIRECTOR, DUKE TRANSLATIONAL RESEARCH INSTITUTE, PROFESSOR OF SURGERY, DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NC

Mr. SULLENGER. Thank you for that introduction, Senator Burr, and good morning, Chairman Alexander, Ranking Member Murray and other committee members. I would like to thank you for the opportunity to share with this committee my perspective as an academic biomedical researcher working on the front lines of medical innovation.

In addition to being an innovator and entrepreneur, I help other faculty at Duke University apply their medical innovations to human health in my role as director of the Duke Translational Research Institute. This institute provides preclinical and early stage clinical trial seed funding and project management support to build collaborative, translational research teams.

I was trained really as a basic scientist in one of the pre-eminent biochemistry labs in the world, Dr. Cech's lab at the University of Colorado, with a goal of pursuing knowledge for the sake of knowledge. However, in 1994, I sought a new career path and focused on what came to be known subsequently as translational research.

I joined the faculty in the Department of Surgery at Duke so I could work closely with physicians and surgeons to develop new approaches to effectively and safely treat the patients they saw every day. During the past two decades, this unorthodox career has been incredibly rewarding. Unfortunately, it has also become increasingly challenging.

With cardiologists, cardiothoracic surgeons, and neurosurgeons, we invented new ways to deliver rapidly reversible anticoagulants for the potential treatment of cardiovascular disease and stroke patients. I work with surgical and medical oncologists to develop new classes of compounds to precisely deliver cytotoxic agents to prostate, pancreatic, and other types of cancers.

Most recently, working with rheumatologists, we invented novel anti-inflammatory agents for the treatment of lupus, arthritis, and other chronic inflammatory disorders without serious side effects. As you can see, we've been very busy, but there's so much more that we could be doing.

Creativity and ingenuity are not limiting. What is preventing these ideas from becoming realities is ever dwindling resources. All of the preclinical work leading to these medical innovations I described was possible because of funding by the NIH and its associated Institutes.

With a 20-plus percent decline in the purchasing power of the NIH budget over the past decade, it has become increasingly challenging to create a path to move these inventions from the bench to the clinic. Moreover, it's challenging to move these inventions from the academic setting to the private sector. It is difficult to obtain investments from the private sector for IND enabling or preclinical enabling work such as compound optimization, preclinical pharmacology, and toxicology and manufacturing.

I applaud the NIH and Congress for recognizing this translational bottleneck and for establishing the Clinical and Translational Science Award program and the National Center for Advanc-

ing Translational Sciences to begin to address this critical issue. In addition, the NHLBI and the NCI and other institutes at the NIH have established some programs, such as the NHLBI network for Translational Research Centers for treating Thrombotic and Hemostatic Disorders, that supports translation of basic sciences into clinical applications.

These new initiatives are critical for our success and will be essential if the United States is to remain the international leader in medical innovation.

Finally, precision medicine, as you mentioned, Senator Alexander, is the future of medicine. Yet it is a major challenge to all of us who translate basic science into health care. This new frontier in medicine combines the information age, which is upon us, with the ability to look at personalized genomics to really collect unparalleled intelligence on health and disease as well as to help us identify what therapies may help each one of us.

To meet these challenges and opportunities head on, we will need to reposition and train a new generation of biomedical researchers that looks very different from the one we have today. Engineers, physicians, mathematicians, and biologists will need to come together as a team to effectively combat disease, disability, aging, and death.

I would suggest there are four tractable issues that we should work on together. No. 1, is how to train and expand a biomedical research workforce that is ready to utilize this genomic and informatics revolution that is underway. No. 2, is how to rebalance and right-size the support of all phases of biomedical research as we transition from gathering intelligence on health and disease through basic research to rationally using those large amounts of research that we've obtained to combat disease through translational and clinical research.

No. 3, is how to reduce the administrative and compliance burdens upon investigators and academic institutions to reduce costs and improve productivity. And, finally, No. 4, is how to further encourage academic institutions like mine to more effectively engage with the private sector.

Thank you.

[The prepared statement of Mr. Sullenger follows:]

PREPARED STATEMENT OF BRUCE A. SULLENGER, PH.D.

Thank you for the introduction Senator Burr and good morning Chairman Alexander, Ranking Member Murray and other committee members. I would like to thank you for the opportunity to share with this committee my perspective as an academic biomedical researcher working on the front lines of medical innovation. In addition to being an innovator and entrepreneur, I help other faculty at Duke University apply their medical innovations to human health in my role as director of the Duke Translational Research Institute. This Institute provides preclinical and early stage clinical trial seed funding and project management support to build collaborative, translational research teams (*https://www.dtmi.duke.edu/about-us/organization/duke-translational-research-institute/pilot-program/leadership*).

I was trained as a basic scientist in one of the pre-eminent biochemistry laboratories in the world, Dr. Cech's lab at the University of Colorado with a goal of pursuing knowledge for the sake of knowledge. However in 1994, I sought a new scientific path and focused on what came to be known as "translational research." I joined the faculty in the Department of Surgery at Duke so I could work closely with physicians and surgeons to develop new approaches to effectively and safely treat the patients they saw every day. During the past two decades, this unorthodox ca-

reer path has been enormously rewarding. Unfortunately, it has also become increasingly challenging.

With cardiologists, cardiothoracic surgeons and neurosurgeons, we invented new ways to deliver reversible anticoagulants for the potential treatment of cardiovascular disease and stroke patients. I also worked with surgical and medical oncologists to develop new classes of compounds that precisely deliver cytotoxic and immune-modulatory medicines to prostate, pancreatic and other types of cancer cells. Most recently working with rheumatologists we invented a novel anti-inflammatory drug for the treatment of lupus, arthritis and other chronic inflammatory disorders without serious side effects.

We have been busy but there is so much more we could be doing. Creativity and ingenuity is not in short supply. What is preventing these ideas from becoming realities are ever dwindling resources. All of the preclinical work leading to the medical innovations I described was possible because of funding by the NIH and its associated institutes. With a 20 percent decline in the purchasing powers of the NIH budget over the past decade, it has become increasingly challenging to create a path to move these inventions from the bench top to the clinic. And moving these inventions from an academic setting to the private sector has become even more challenging and rate limiting. It is extremely difficult to obtain investments from the private sector for IND (Investigational New Drug) enabling work such as compound optimization, preclinical pharmacology and toxicology studies and manufacturing. I applaud the NIH and Congress for recognizing this translational bottleneck and for establishing the Clinical and Translational Science Award (CTSA) program and the National Center for Advancing Translational Sciences (NCATS) to begin to address this critical issue. In addition, the NHLBI, NCI and other institutes at the NIH have established some programs such as the NHLBI national network of Translational Research Centers for Thrombotic and Hemostatic Disorders that supports the translation of basic sciences into clinical applications. These new initiatives are critical for our success and will be essential if the United States is to remain the international leader in medical innovation.

Finally, precision medicine—the future of medicine—is a major challenge to all of us who translate basic research into health care. This new frontier in medicine combines the information age with personalized genomics to collect unparalleled intelligence as to what makes us sick and what therapies can be tailored to each of us. To meet these challenges—and opportunities—-head on, we will need to reposition and train a new generation of the biomedical researchers. This next generation will look very different from the one we have today: Engineers, physicians, mathematicians, and biologists will need to come together to effectively combat disease, disability, aging and death.

To prepare for the coming challenges, I would encourage this Senate Committee to work with the NIH, FDA, academic community and private sector to consider four tractable issues:

1. How to train and expand a biomedical research workforce that is ready to utilize and act upon the genomic and informatics revolution;
2. How to rebalance and right size support for all phases of biomedical research as we transition from gathering intelligence on health and disease (basic research) to rationally using the large amounts of information to combat disease (translational and clinical research);
3. How to reduce the administrative and compliance burdens placed upon investigators and academic institutions to reduce costs and improve productivity; and
4. How to further encourage academic institutions to more effectively engage with the private sector and clarify the NIH conflict of interest policy to facilitate such endeavors without restricting innovation.

REFERENCES

REFERENCES REGARDING THESE CONSIDERATIONS

1. How training should be expanded to create a biomedical research workforce that is ready to utilize and act upon this emerging information;

References describing strategies to revise the training of the biomedical workforce and how team science will be important for translational medicine.

- *https://www.aau.edu/WorkArea/DownloadAsset.aspx?id=15491*;
- *http://www.hhmi.org/programs/med-into-grad-initiative*;
- *https://www.dtmi.duke.edu/about-us/organization/duke-translational-research-institute/pilot-program/leadership*; and
- *http://www.pnas.org/content/111/16/5773*.

2. How to rebalance and right size support for all phases of biomedical research as we transition from gathering intelligence on health and disease (basic research) and move toward rationally applying the large amounts of information being amassed to combat disease (translational and clinical research);

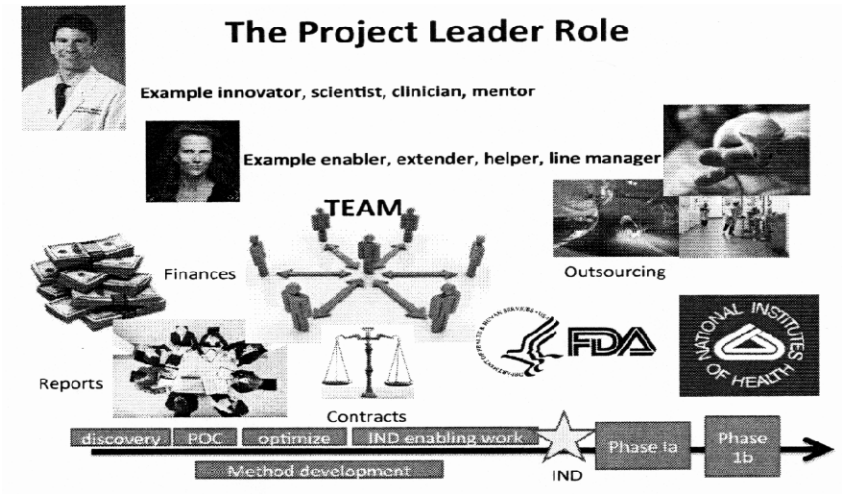
Breakdown in basic versus applied funding from the NINDS.

- *http://blog.ninds.nih.gov/2014/03/27/back-to-basics/*.

3. How to reduce the administrative and grant writing burden upon translational investigators and academic institutions to reduce costs and improve productivity; and

Link to DTRI Project Management and Consultation Office which offers professions trained in the private sector to act as faculty extenders and facilitate translational team builders.

- *https://www.dtmi.duke.edu/research-facilities-and-support/duke-translational-research-institute-dtri/project-management*.



4. How to further encourage academic institutions to more effectively engage with the private sector and clarify the NIH conflict of interest (COI) policy to facilitate such endeavors without restricting innovation.

Links to NIH COI policy and the Duke's approach to complying with the policy:

- *http://grants.nih.gov/archive/grants/policy/coi/tutorial/fcoi.htm*; and
- *http://duke.edu/services/ethicscompliance/coi/fcoi/index.php*.

The CHAIRMAN. Thank you, Dr. Sullenger.

We'll now go to Mr. Borisy.

STATEMENT OF ALEXIS BORISY, PARTNER, THIRD ROCK VENTURES, BOSTON, MA

Mr. BORISY. Good morning, Chairman Alexander, Ranking Member Murray, and members of the committee. My name is Alexis Borisy, and I am a partner at Third Rock Ventures.

At Third Rock, our mission is to form, launch, and build great companies in areas of disruptive science and medicine to discover and develop new products that will make a meaningful difference for patients, physicians, and our healthcare system overall. I applaud this committee for its commitment to advancing research and development for patients.

Part of what makes life science innovation so successful here in America is the functioning of the entire innovation ecosystem from basic research to venture and industry investment in early discovery through extensive investment in development and then to

commercialization. The development of modern medicines and technologies from the handoff of basic research onward is a risky and expensive endeavor, taking over a decade and more than a billion dollars to deliver a single new product.

But there can be no question of the reward. Over the past decades, we have provided medicines and technologies that have vastly improved the quality and longevity of the lives of patients.

The current conditions for private investment into life sciences are strong in many areas, but also difficult in others. Policy actions have strengthened the investment into areas such as therapeutics for oncology and rare genetic diseases, while conditions have challenged other areas such as devices and diagnostics.

Overall, venture investments in 2014 in the life sciences has been the highest since 2008. One must note that although therapeutics venture investments are robust, medical devices and diagnostics have not fared as well, and first-time investments into new companies has fallen last year to the lowest number since 1995. A primary reason for this decline is the increased time and cost of developing new devices and diagnostics with an increased uncertainty about reimbursement once on the market.

Looking forward, I must note that a keystone to ensuring a robust life sciences industry is a national commitment to supporting basic research. Our Nation's historical commitment to life sciences basic research is viewed as a precious jewel among nations. However, funding for the NIH has been effectively declining for the past years.

Basic research is the key to unlocking the mysteries of diseases and providing foundational discoveries that enable the venture and biopharmaceutical industry to ultimately develop new medicines for patients. It is a long, expensive, and risky road from basic research to breakthrough medical products. Investors and industry are willing to make those investments and take on those risks, but the investments and risks cannot be made without the substratum in basic research to start from.

Building from basic research, venture funding is the life blood of the small biotechnology companies working on disruptive science. These venture-backed small biotechnology companies are the life blood of innovative new medicines. The decision to deploy capital is directly impacted by the regulatory decisions and behaviors. Better enabling and encouraging FDA to utilize flexible approaches has had a very positive impact on venture funding.

The 41 novel new drugs approved last year, in part reflecting the successes of accelerated approval and breakthrough therapy designations, is a substantial positive signal for innovation. Investments in early stage potentially breakthrough innovation in life sciences follow these signals, and venture investment in rare genetic disease and oncology remains very strong and has been increasing.

It is important to note the positive effect that steady leadership over these past recent years has had at the FDA. I cannot underscore enough the importance to the venture community of having stable, long-term leadership at the agency. It is also important to note the positive effect that policy initiatives, such as breakthrough therapy, have had and its successful implementation in some areas.

As a society, while we celebrate these successes, we have to ask ourselves about what we want to do to improve how we treat some of the other egregious diseases that affect some of our citizenry, including obesity, diabetes, Alzheimer's, depression, antibiotic resistance, as well as many others. As we examine the successes of the programs I mentioned before, we should endeavor to learn from the flexible and modern approaches utilized under those programs and work to apply them more broadly across therapeutic areas.

Recent ideas such as approval based on identified subpopulations in Europe's adaptive licensing pilot could serve to modernize our current system. Limited population approval could make a significant difference, not only for antibiotic resistance, but for many subpopulations of disease.

We need to incorporate the perspective of the patients closely and make sure that we are examining the right benefits and risk tradeoffs. These approaches could serve to ensure that the right drugs are getting to the right patients in a much more effective manner.

Thank you for the opportunity to provide my testimony.

[The prepared statement of Mr. Borisy follows:]

PREPARED STATEMENT OF ALEXIS BORISY

Chairman Alexander, Ranking Member Murray, and members of the committee, my name is Alexis Borisy, and I am a partner at Third Rock Ventures. Our firm's mission is to build great companies that discover and develop products that make a difference for the patients we serve. Our work focuses on forming, launching, and building innovative companies in areas of disruptive science and medicine, and matching that to the right business and strategy. We work to advance pipelines of discovery projects to the clinic and develop new products that will make a meaningful difference for patients, physicians, and our healthcare system overall. I personally have over 20 years of experience in building and operating innovative science-based companies and currently am chairman of the board and co-founder of NASDAQ-listed foundation medicine, chairman of Warp Drive Bio, director for Blueprint Medicines, which I co-founded, and director for Editas Medicines and Revolution Medicine. I also serve on the board of the National Venture Capital Association and was formerly on the board of the Biotechnology Industry Organization.

I applaud this committee for its commitment to advancing research and development for patients. Our understanding of diseases and how we develop medicines has advanced tremendously over the last 20 years. With over 3,400 medicines in development and over 2,000 public and private companies in the United States, the promise of this industry for our society is great.[3] We have the potential to transform how we treat patients with life-threatening and chronic diseases, a goal that not only would improve the lives of patients and their families, but create new solutions to our Nation's most pressing health care needs. We must work together to ensure the United States' biopharmaceutical and medical device and diagnostic industries are best equipped to maintain global leadership and empowered to deliver the next generation of medicines and therapies.

This hearing is focused on the critical components of fostering continued investments in research and development and advancing therapies for patients. America's leadership in this space historically has led to translation of cutting edge science, medicine, and technology into products that manage or treat medical conditions that otherwise would decrease quality of life and productivity for Americans. There is much that has been done right in the past few years to encourage this investment into companies focused on breakthrough science and its application to products. Yet there are also areas of significant opportunities to improve, and the patients are waiting.

It is important to understand that successful development of new medicines, devices, and diagnostics is dependent on policies that support the entire life science ecosystem—beginning with basic research and ending with providing treatments and therapies to patients. Disruption or weakening of policies that negatively impact any part of this ecosystem weakens the entire enterprise. Part of what makes life sciences innovation so successful here in America is the functioning of this en-

tire ecosystem, from basic research, to venture and industry investment in early discovery, through extensive investment in development, and then to commercialization.

Assuming that a strong foundation of societal investment in basic research exits, the development of modern medicines and technologies from that point onward is a capital- and time-intensive endeavor taking an average of 10 years and $1 billion to deliver a single new drug.[3] It is also a high-risk endeavor involving finding solutions to complex scientific and medical problems. However, when successful there can be no question of the reward. Over the last 20 years we have provided medicines that have vastly improved the quality and longevity of lives for patients dealing with diseases such as HIV/AIDS, cancer, and heart disease.

The current conditions for private investments into life sciences are strong in some areas but difficult in others, and I will attempt to exemplify in my comments how policy conditions have strengthened investment into some of these areas, such as therapeutics for oncology and rare genetic diseases, while conditions have challenged other areas such as devices and diagnostics.

In general terms of first-time financings, industries that captured the highest total of venture capital dollars and deals in 2014 were software, media and entertainment, and biotechnology. Overall, investments in 2014 in the life sciences sector, both Biotechnology and Medical Devices combined, rose to the highest level since 2008 with $8.6 billion invested into 789 deals. While there was a 29 percent increase in dollars there was also a 3 percent drop in deals compared to 2013. Dollars invested into life sciences companies accounted for 18 percent of total venture capital investments in 2014. Venture capitalists alone invested $6 billion into private biotechnology companies.

These private investments trends are a result of a positive regulatory and policymaking environment for the biotechnology and pharmaceutical arenas, with one particular example being the success of FDA's Breakthrough Therapy Designation. Medical device and diagnostics did not fare as well, as venture capitalists invested $2.6 billion in private medical device companies in 2014, down more than 27 percent from the 2008 peak of $3.6 billion. Of even greater concern, first-time investments into medical device companies tell an even starker story. In 2014, there were only 58 medical device companies that raised their first round of venture capital financing, the lowest number of companies since 1995. A primary reason for this decline is the increased time and cost of developing new devices coupled with an increased uncertainty about reimbursement once on the market.

THE UNITED STATES MUST COMMIT TO FUNDING DISCOVERY

A keystone to ensuring a robust life science industry is a national commitment to support basic research. Our nation's historical commitment to life sciences basic research is viewed as a precious jewel among nations. However, funding for the National Institutes of Health has been directly or effectively declining for the past several years with decreased or flat budgets that have not recognized inflation.[4] Basic research is the key to unlocking the mysteries of diseases and providing foundational discoveries that enable the biopharmaceutical industry to continue to research and ultimately develop new medicines for patients. It is a long, expensive, and risky road from basic research to a breakthrough medical product, and investors and industry are willing to make those investments and take on those risks, but the investments and risks cannot be made without the substratum in basic research to start from. Diminished support for basic research will lead to a smaller pipeline of next-generation medicines and impede our country's potential to transform how we treat diseases.

Research dollars provided by the National Institutes of Health to universities and colleges throughout the country also serve to train future scientists for jobs of the future. Currently, the U.S. biomedical research sector supports over 5 million high-paying jobs in the United States and has tremendous potential for growth.[5] However, we must understand that our position as the global leader in medical science is constantly being challenged, and without a sustained commitment for scientific discovery, this is not a position that will be maintained.

ENABLING ADOPTION OF MODERN APPROACHES TO DRUG, DEVICE AND DIAGNOSTIC DEVELOPMENT & APPROVAL WILL INCENTIVIZE INVESTMENT

Venture funding is the life-blood of the small biotechnology companies working on disruptive science, and these venture-backed small biotechnology companies are the life-blood of innovative new medicines. In fact, a study published in 2010 found that in the United States a majority of scientifically innovative drugs were discovered or developed by biotechnology companies.[6] Large pharmaceutical companies may take

over late-stage development and commercialization of many small biotech drug development programs.

However, without innovative small biotech companies, many of today's innovative medicines would not exist, which in turn would not exist without the early-stage venture capital funding.

The decision to deploy capital is directly impacted by regulatory decisions and behaviors. Better enabling and encouraging FDA to utilize flexible approaches reflective of our understanding of the disease and patient being treated, as well as incorporation of modern approaches to development and approval, have a positive impact on venture funding. For example, since the implementation of the Accelerated Approval pathway in 1992 over 80 drugs have been approved utilizing this pathway, including 29 to treat cancer and 32 to treat HIV.[7] This pathway allows for approval based on surrogate endpoints such as shrinking tumors or decreasing viral loads indicative of clinical benefits to patients with a commitment by the company to conduct confirmatory trials post-market to confirm the benefit. This has allowed oncology and HIV drugs to enter the public market in a significantly more effective manner. It is no coincidence that oncology has been and is projected to be one of the most active and innovative therapeutic markets.[8]

Likewise, in recent years FDA has shown an increased willingness to work with companies to develop more effective clinical development programs for rare diseases. This, along with added exclusivity for orphan drugs, has led to a significant increase in venture investment in rare diseases. The results are clear. In 2012, FDA reported that from 2007 to 2012 approximately one-third of the NMEs (New Molecular Entities) approved were drugs for rare diseases.[9] This trend continued in 2013, when 33 percent of NMEs approved were drugs to treat rare diseases.[10] Again, we see that investment in early stage, potentially breakthrough innovation in life sciences follows these signals, as venture investment in rare genetic diseases has significantly increased over the past few years.[11]

We have seen continued commitment from FDA and policymakers to work on ensuring an effective development and review process. In fact, in 2014, the FDA approved 41 novel new drugs the highest number of novel drugs approved in the past 10 years. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) created a new Breakthrough Therapy designation that provides increased interactions with FDA to ensure the most effective development and approval processes for promising new treatments. As of February 2015 there have been 80 breakthrough designations granted by FDA.[12] Similar to statistics for accelerated approval, many of these designations have been given to oncology and rare disease treatments and therapies.[13]

It is important to note the positive effect that steady leadership over these past recent years has had at the FDA, and I cannot underscore enough the importance to the venture community of having stable, long term leadership at the agency. It is also important to note the positive effect of policy initiatives such as Breakthrough Therapy, and its successful implementation in some areas. Currently, FDA is in the process of implementing these improvements. Ensuring FDA can hire, retain, recruit and has tools to ensure the organization is best able to carry out its mission is also critically important.

The benefit of these programs has clearly been mostly realized in the oncology and rare disease space. Much has been written regarding the enormous increase in requirements, duration, and expense of clinical trials.[14 15 16 17] These increases are especially acute for drugs designed to treat chronic diseases with larger patient populations. As a consequence, the cost and regulatory uncertainty of developing drugs for these populations has been increasing, and we must ask if there is more we could do to get these potential therapies to patients.

As a society, while we celebrate the incredible successes, and indeed we *should* celebrate these successes, we have to ask ourselves what we want to do to improve how we treat some of the other egregious diseases affecting great numbers of our citizenry and long-term health costs, such as obesity, diabetes, Alzheimer's, and depression among others, as well as pressing issues such as antibiotic resistance. As we examine the successes of these programs in terms of number of approvals for cancer and rare genetic diseases, we should endeavor to learn from the flexible and modern approaches utilized under these programs and work to apply them more broadly across therapeutic areas.

The fact is that while there are several examples where FDA has allowed for the utilization of novel endpoints, advanced tools such as biomarkers, and non-traditional clinical trial designs, the basis for such decisions is still poorly understood and inconsistent across review divisions. Without a more transparent and consistent approach as to what criteria such decisions are based on, the private sector will be hesitant to develop or utilize advanced approaches. Guidance from and involvement

of FDA are critical to creating processes for data collection to support the utilization and adoption of novel endpoints and modern drug development tools and approaches would incentivize investment and enable a modern and effective approach to drug development and review.

However, while there is a lot to be excited about when it comes to the number of FDA approvals and programs discussed above, when it comes to chronic diseases with varying stages of progression and severity, there seems to be an actual reticence to employ modern tools and approaches. Recent ideas such as approval based on identified subpopulations, and Europe's adaptive licensing pilot could serve to modernize our current system.

Limited population approvals could make a significant difference, not only for antibiotic resistance, but for many subpopulations of disease. Currently, our regulatory system is based on a philosophy that more information before approval is better. We must always support the highest standard of safety, but we must advance to a system that critically examines information required and determine whether it is actually informative as to the potential success of the drug in the real world. Creating approval pathways that enable the development of drugs for subpopulations of patients in areas like Alzheimer's, diabetes, and antibiotic resistance could be a game-changer. We need to incorporate the perspective of the patients closely, and make sure that we are examining the right benefit and risk tradeoffs. These approaches could serve to ensure the right drugs are getting to right patients in a much more effective manner.

From early stage life sciences venture investment perspective, we know that when we start a company with breakthrough innovations in new areas of science and medicine it will take a long time to turn that innovation into a drug that will reach patients and physicians and improve public health. The reality is the time required to put a drug on the market is, more often than not, longer than the length of our investment funds. Thus, when we create a new innovative company in a new area of science and medicine we are counting on the new medicine being developed being seen as important and valuable when it is still in the early stages of development. This is often referred to as the "proof of concept in the clinic," or Phase IIA. At that point, we are counting on the company and the product being sufficient to either take the company public on the NASDAQ or to have the company and/or product acquired by a pharmaceutical or larger biotech company.

The modern approach to regulation that exists now for cancer and rare genetic diseases allows this to work very well for three reasons. First, the regulatory process is more interactive, flexible, and reflective of the disease and patient being treated. Second, the amount, of time, and size of investment required to fund a company through "proof of concept" is better understood. And, third, the next steps in our innovation ecosystem, larger companies and public investors, value the early stage proof of concept data because they feel more confident about the development and approval process for these drugs. However, the same cannot be said for diseases such as obesity, diabetes, and Alzheimer's, where the time, amount of funds, and regulatory requirements are greater and there is less understanding about how to utilize modern tools and approaches. Without improving these processes, it is very difficult to imagine how early stage investment can occur in such important areas.

In addition to understanding the criteria needed for FDA to allow for utilization of modern tools, such as biomarkers and diagnostics—which are key to advancing personalized medicine by enabling the ability to diagnostically define subsets of patients suffering from a disease—there is also a need to provide incentives and clarity for the development of such tools. This is particularly important for the development of new diagnostics. It is imperative that regulatory processes for personalized medicine encourage early collaboration for the approval of therapeutics and companion diagnostics, as well as the development of advanced diagnostics in general. Furthermore, the lack of clarity around approval of advanced molecular diagnostics, coupled with an enormous lack of clarity on reimbursement for them once approved, has been making investment into this necessary space to recognize the vision of precision medicine quite challenging.

A key barrier to the advancement of diagnostic development is the fact that there are no consistent reimbursement policies for diagnostics. Last year, Congress passed the Protecting Access to Medicare Act of 2014 which included the Improving Medicare Policies for Clinical Diagnostic Laboratory Tests provision. This provision is an important and positive step forward. How transformative depends on whether the potential benefits of this provision are realized and implemented in the regulations. There remains substantial uncertainty in the private and public world of reimbursement for molecular diagnostics.

This uncertainty continues to hold back investment in breakthrough personalized medicine innovation that could significantly advance how we develop drugs and

treat patients with critically important diseases such as Alzheimer's, diabetes, and others. Lack of regulatory clarity coupled with lack of clarity on reimbursement also limits investment in medical devices. For both diagnostics and devices, it may take 2–5 years after the product is approved to secure reimbursement. This uncertainty is a significant factor in limiting investment. A recent NVCA survey found that regulatory concerns were cited as the No. 1 reason investors were moving away from putting funds into medical technology companies.

There are two more areas critical to modernizing our approach to developing medicines and ensuring continued investment in new solutions that will benefit patients. We must strengthen the ability to integrate patient perspectives in the drug development and review process. The ability to provide information about patients' perspectives about their diseases and what they believe to be benefits or acceptable risks would help ensure that the medicines being developed are seen as helpful to the patients they are being designed to treat.

Protection of intellectual property and patents is also paramount. Patents are the only asset a small company has to attract investment. If patents are weakened, the already high-risk proposition becomes one that is too much and investment in this industry will be decimated. We must ensure that the patent system protects the patent owners, abuses of the system for sheer monetary gain and not the advancement of science and discovery should not be supported.

Last, we must ensure that reimbursement policies are determined in the context of the disease and patient being treated and the impact of a drug is evaluated over appropriate time lines. With regard to devices and diagnostics we must make the same policy strides as we have in other medical spaces. Appropriate Federal investments and a robust and transparent and predictable process for approvals will allow for increased private investments. We must not create a system that will severely diminish investment in the next generation of cures and treatments.

Thank you for the opportunity to provide my testimony on this important topic. There are other critical policy areas that have the ability to impact or weaken the life science ecosystem not mentioned in this statement, but I would be happy to discuss these areas further with this committee.

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The CHAIRMAN. Thank you, Mr. Borisy.

Mr. Mussallem.

STATEMENT OF MICHAEL A. MUSSALLEM, CHAIRMAN AND CEO, EDWARDS LIFESCIENCES, IRVINE, CA

Mr. MUSSALLEM. Chairman Alexander, Ranking Member Murray, and members of the subcommittee, thanks very much for taking on this important subject. It's very meaningful.

I'm Mike Mussallem. I'm the chairman and CEO of Edwards Lifesciences. I'm here representing AdvaMed and the hundreds of thousands of U.S. medical device industry employees who are passionate about helping patients, and I'm truly honored to join my fellow panelists today.

We should all be concerned that innovation in the United States is suffering from a costly, cumbersome, and risk-averse regulatory system. I'm privileged to lead a company that's been the world leader in developing and manufacturing heart valve replacements for more than 50 years.

Our recent experience in a transformational therapy to replace heart valves has given us a unique perspective on the current climate. This technology allows a heart team to deliver a collapsible prosthetic valve into the body via a catheter, thus avoid cracking the chest, stopping the heart, and a long and painful recovery.

This is the most extensively studied heart valve, including an unprecedented four New England Journal of Medicine publications, that demonstrated a triple win, a substantial and sustained clinical benefit, cost effectiveness, and extraordinary quality of life enhancements. Unfortunately, the United States was the 42d country to get this new technology, 4 years after Europe.

Since then, Dr. Shuren and the leadership of FDA have been working to improve the regulatory pathway, and they've made commendable progress in this area, including facilitating early feasibility trials in the United States, enabling more rapid approvals of next-generation therapies, and using post-market registry data to expand patient access. Additionally, this breakthrough technology benefited from a close collaboration between FDA and CMS so that when new patient populations were approved, they were immediately covered by Medicare.

If these techniques and the others in AdvaMed's innovation agenda could be applied to other technologies more broadly, that would go a long way toward revitalizing innovation in the United States.

We see several additional opportunities to remove barriers. First, FDA's vision to improve the regulatory process must be accelerated. FDA has recently proposed a number of improvements to the pre-market clinical trial process and post-market surveillance. For example, improving the process to incorporate patients' perspectives on risk tolerance is an important step in the right direction.

In addition to these regulatory enhancements, we believe there should be a separate breakthrough technology designation for transformative therapies to receive preferential regulatory treatment. We also believe a central investigational review board could reduce the cost and delays of initiating clinical trials.

Second, we should strengthen the R&D infrastructure such that it is second to none. We support steady growth of funding to the NIH and the National Science Foundation. Additionally, the SBIR and tech transfer programs can be improved by raising the amount

of funding to better recognize the costs actually incurred by startup companies.

Third, to encourage innovation, there are a few essential elements for a robust ecosystem that rewards our unique American culture of innovation: ready access to capital, timely and predictable regulatory processes, a reimbursement system that supports promising therapies as they go through their iterative improvement process, and a strong intellectual property protection. In addition, the United States needs to foster a supportive business environment through tax policies that encourage the development of high-wage and high-value industries like the medical device industry.

Finally, no discussion about medical technology is complete without understanding the true impact that medical advancements have on patients, and we are fortunate to meet a lot of patients. Earlier this month, we welcomed more than 100 heart valve patients and caregivers to Edwards to connect and support one another and learn how they can use their voice to help other patients.

I met a woman from Colorado who survived Hodgkin's lymphoma only to find out that she needed a heart valve replacement. Thanks to transcatheter heart valve therapy, her radiation-damaged chest did not have to be opened, and today she is doing well and back to work as a middle school teacher.

It's patients like these, ranging in age from teenagers to folks in their nineties, that remind us daily that our work is personal and impacts people individually. We welcome your support to remove the barriers to innovation that may delay patient access to life-saving therapies developed and made right here in America.

Thank you.

[The prepared statement of Mr. Mussallem follows:]

PREPARED STATEMENT OF MICHAEL A. MUSSALLEM

SUMMARY

I am here because I am passionate about helping patients. That's why I and hundreds of thousands of U.S. medical device industry employees like me come to work each day. We love what we do because it can have such an amazing, direct impact on the lives of patients.

But the balanced ecosystem that has supported medical innovation in the United States has been eroded by an increasingly costly and cumbersome regulatory process, and a risk-averse payment culture. Based on Edwards Lifesciences' experience in developing and delivering new therapies to American patients over the last several decades, I am very concerned that we are seeing an alarming decline in U.S. medical innovation.

As an innovator, Edwards has the unique opportunity to live and breathe the current regulatory process on a daily basis. Our experience with transcatheter aortic heart valve replacement (TAVR), a revolutionary approach to replacing a patient's aortic heart valve without open-heart surgery, has provided us a unique perspective on the current state of the regulatory process. On behalf of the AdvaMed, the Advanced Medical Technology Association, today I will focus on three primary areas:

1. FDA's vision to improve the regulatory process must be accelerated.
2. We should strengthen the R&D infrastructure so that it is second to none.
3. To encourage innovation, we need to address issues throughout the entire ecosystem.

FDA has made improvements to the regulatory approval process over the past few years. In particular, progress has been made with TAVR therapies, including early feasibility trials in the United States, approvals of new generations of TAVR therapies, and the use of registry data to expand patient access. My testimony will touch on how FDA can apply these improvements, and other concepts put forward by AdvaMed in our Innovation Agenda, to provide innovators and entrepreneurs with the incentives to make investments in new, breakthrough therapies. It will also ac-

knowledge a robust research and development infrastructure is a critical component of the innovation ecosystem. Finally, it will outline ideas on fostering an ecosystem that incentivizes curiosity and rewards innovators.

At Edwards, patients help remind us daily that our work is personal. Each heart valve represents a patient and their family, who otherwise would miss out on both the extraordinary and precious experiences of their daily lives. We encourage you to ensure that our healthcare system listens carefully to the patient's voice, and look forward to continuing to work with you to support a vital U.S. innovation ecosystem that addresses patients' needs.

INTRODUCTION

Chairman Alexander, Ranking Member Murray and members of the committee, I am Mike Mussallem, chairman and CEO of Edwards Lifesciences, based in Irvine, CA, and I am testifying today on behalf of AdvaMed, the Advanced Medical Technology Association. I am truly honored to join my fellow panelists today to discuss a path to revitalizing medical device innovation in the United States.

I am here because I am passionate about helping patients. That's why I and hundreds of thousands of U.S. medical device industry employees like me come to work each day. We love what we do because it can have such an amazing, direct impact on the lives of patients.

Based on Edwards' experience in developing and delivering new therapies to American patients over the last several decades, I am very concerned that we are seeing an alarming decline in U.S. medical innovation.[1] The balanced ecosystem that has supported innovation in the United States has been eroded by an increasingly costly and cumbersome regulatory process, and risk-averse payment culture.

The United States has been the world leader in medical technology for more than a generation, but our leadership is eroding. Venture capital investment, especially investment in the early stage ideas that are the future of innovative therapies, has plummeted—a decline of almost three-quarters between 1997 and 2013.[2] While the current FDA leadership has begun to make dramatic improvements, the regulatory process remains time-consuming, inefficient, and unpredictable. The payment environment is far less hospitable to new technology today than ever before, meaning investment in new treatments is discouraged and patients are deprived timely access to important new therapies. Additionally, uncompetitive tax policies disincentivize the location of R&D and manufacturing in the United States.

Over the 35 years I have spent working in medical devices, I have had the opportunity to be involved with the development of dozens of innovative therapies. Today, I am privileged to lead the more than 9,000 employees of Edwards Lifesciences, who dedicate their lives in a very personal way to helping critically ill patients and those suffering from heart valve disease around the world. We have been the leaders in heart valve innovation for more than 50 years, starting when an engineer, Miles Lowell Edwards of California, partnered with a cardiac surgeon, Dr. Albert Starr of Oregon, to develop the first commercially available artificial heart valve. I also had the honor of representing our industry in a number of leadership roles, noteworthy among them my term as chairman of our trade association, AdvaMed.

It is my experience that successful medical device innovators keep an unwavering focus on patients. We count it a privilege to serve these patients, creating and supplying devices and therapies that save, enhance and prolong lives. We are the toolmakers for clinicians, working closely with them to develop technologies to address unmet patient needs. Each new innovation is also a stepping stone that lays the path to something even better. Innovation is a powerful and iterative force, and those who are involved in it are never satisfied with the status quo. It is our passion and mission to keep finding better solutions to improve human health.

Edwards' innovation story is similar to many companies that have made medical technology a uniquely American success story. The medical technology industry is central to the development of devices and diagnostics that will provide the life-saving and life-enhancing treatments of the future. Patient access to advanced medical technology generates efficiencies cost savings for the health care system and improves the quality of patient care. Over the last three decades (between 1980 and

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[1] National Venture Capital Association. (2014). NVCA 2014 Yearbook. Arlington, VA: Thomson Reuters.

[2] PWC and National Venture Capital Association, "Venture Capital Investments Q1. 2014—Money Tree Results," April, 18, 2014. There was an increase in 2014 from the low of 2013, but much of the increase was concentrated in digital health, informatics and self-pay technologies, leaving potential technological breakthroughs to diagnose and treat major diseases still starved for resources.

2010), advanced medical technology helped cut the number of days people spent in hospitals by more than half and added 5 years to U.S. life expectancy while reducing fatalities from heart disease and stroke by more than half.

The industry is also an engine of economic growth for the United States, generating high wage manufacturing jobs and a favorable balance of trade. Medical technology is responsible for more than two million U.S. jobs, including both direct and indirect employment.[3] Clusters of innovation in States like California, Texas, Minnesota, Massachusetts, New York and North Carolina, are responsible for addressing the world's most serious health challenges, while, at the same time, serving as a robust economic engine, providing attractive U.S. jobs and economic growth far into the future.

As innovators, we have the unique opportunity to live and breathe the current regulatory process on a daily basis. Our experience with transcatheter aortic heart valve replacement (TAVR), a revolutionary approach to replacing a patient's aortic heart valve without open-heart surgery, has provided us a unique perspective on the current regulatory process. As we have navigated the regulatory channels to bring this therapy to U.S. patients over the last decade, we have taken note of not only the challenges, but also the forward-looking vision of the leaders of FDA and CMS to develop opportunities for better collaboration with the agencies. FDA has learned from the last several years, and we are already seeing much-needed improvements being made.

We believe opportunities remain to reduce barriers in regulatory approval and reimbursement that will help promote America's continued worldwide leadership in the area of medical device development and support innovation. AdvaMed has proposed a new Innovation Agenda (attached). Enactment of this agenda can unleash the potential of medical technology to extend and improve lives, reduce the cost and burden of disease, and maintain and enhance U.S. scientific and economic leadership. I know the committee shares these same goals and I applaud you for your focus on these important issues. Today I will focus on three primary areas:

1. FDA's vision to improve the regulatory process must be accelerated.
2. We should strengthen the R&D infrastructure so that it is second to none.
3. To encourage innovation, we need to address issues throughout the entire ecosystem.

EDWARDS' UNIQUE PERSPECTIVE

Edwards Lifesciences has been at the forefront of an ambitious effort to impact the lives of patients suffering from a deadly heart valve disease called aortic stenosis. The Edwards SAPIEN transcatheter aortic heart valves deliver a collapsible prosthetic valve into the body via a catheter-based delivery system. The valve is designed to replace a patient's diseased native aortic valve while the heart continues to beat—avoiding the need to saw open the patient's chest, connect them to a heart-lung machine, and stop the heart. Those of you who have a friend or relative who has had open-heart surgery knows first-hand how difficult this procedure and its arduous recovery can be. In fact, it is so invasive that some patients simply cannot have surgery because the risk of death is too high. Our new heart valve procedure allows patients to avoid that pain and suffering.

Some patients who receive the SAPIEN transcatheter valves can leave the hospital and return home the next day. It's extremely gratifying to hear physicians and patients describe the immediate improvement in patients' health after TAVR. They can breathe and speak more easily, their skin transforms from gray to pink as their vital organs once again receive the oxygen-rich blood they need, and their vibrancy returns within hours.

Patients receiving the Edwards SAPIEN valve return home with potential years of good health added on to their lifespan. Extensive study of this valve—including an unprecedented record of four *New England Journal of Medicine* papers—has demonstrated the "triple win": a substantial and sustainable clinical benefit, extraordinary quality-of-life improvement, and cost effectiveness in inoperable patients. In fact, the SAPIEN valves are the most studied heart valve in history. There are more than 3,000 peer-reviewed publications on transcatheter aortic valve replacement (TAVR). There are also more than 60 cost effectiveness studies and at least 30 publications on quality of life related to TAVR.

While our experience with SAPIEN and TAVR, transcatheter aortic valve replacement, has ultimately been successful, it is important to reflect on its unique and challenging regulatory pathway, including some key milestones:

[3] The Lewin Group, "State Economic Impact of the Medical Technology Industry," June 7, 2010 and February 2007.

• In 1999, Edwards began an internal program exploring transcatheter valve replacement.
• In 2002, Professor Alain Cribier performed the first-in-human procedure of a transcatheter aortic valve replacement in France.
• In 2007, the Edwards SAPIEN valve, our first commercial transcatheter heart valve, received CE Mark for European commercial sale. The next-generation SAPIEN XT valve received CE Mark 3 years later.
• Before SAPIEN was approved by FDA, CMS took the unusual step of initiating a National Coverage Determination (NCD) in October 2011.
• Four years after obtaining CE Mark in Europe, and after one of the largest, randomized controlled trials in the history of medical devices, the SAPIEN valve was approved by FDA in November 2011 for the treatment of inoperable patients, making the United States the 42d country in the world to approve the device.
• We received regulatory approval for our second-generation device in 2014 and are working on getting the third-generation approved in the United States in the near future.

We are encouraged to see that FDA leadership has taken the initial device lag experience with TAVR as a catalyst to improve. In fact, the Agency has made significant progress in bringing newer generations of TAVR products to patients faster. They have been very actively engaged with many constituencies in the healthcare system, working to better understand and improve predictability and shorten the approval timeline for future generations of transcatheter heart valve devices. In doing so, the device lag for TAVR has narrowed significantly.

One way FDA has worked to improve the process is to use registry data to expand patient access. Under the TAVR NCD, CMS requires that every U.S. patient be enrolled in a qualified prospective registry that tracks appropriate outcomes data to the patient level. In a remarkable effort of collaboration between the medical societies, regulators and other interested stakeholders, the American College of Cardiology (ACC) and the Society of Thoracic Surgeons (STS) helped build what has become one of the most robust clinical evidence and quality measurement tools ever created: the STS/ACC TVT Registry. In an unprecedented step, data from the STS/ACC TVT Registry for transcatheter aortic valve replacement procedures were used by FDA in 2013 to help expand the indications for use of our SAPIEN technology, allowing access to a broader patient population.

At the same time, through close collaboration between FDA and CMS, when new patient populations are approved, they were immediately covered by Medicare. This collaboration took vision and commitment by both FDA and CMS, and they should be commended for their work. We think that these novel approaches reflect agency views that take promotion of public health as seriously as they take patient protection, which as consumers of the system we should all welcome.

We realize that TAVR is a unique example of a breakthrough technology that perhaps warrants this kind of attention from FDA and CMS. If these techniques can be applied to other technologies more broadly, that would go a long way toward revitalizing innovation in the United States

FDA'S VISION TO IMPROVE THE REGULATORY PROCESS MUST BE ACCELERATED

As noted through the Edwards transcatheter heart valve experience, improvements in the FDA device review process can reduce the time and cost associated with the development and approval of devices and diagnostics. They can also ensure that the CDRH's stated vision—that American patients will be the first in the world to have access to new devices—is achieved, while maintaining the highest standards of safety and efficacy.

One important area where FDA is heading in the right direction is through its efforts to better involve patients in the regulatory process. Specifically, its guidance document and work through the Medical Device Innovation Consortium, to create a framework and catalog of patient preference measurement tools, will help regulators and device sponsors better incorporate patients' perspectives into the approval process. It is frustrating to Americans to hear that Europeans have access to innovations not available in the United States. Many patients have asked me and petitioned our company directly: "It is my life; why can't I make the decision?" The steps that FDA is already taking to listen to the patient perspective can help adjust the regulatory requirements to meet patient demands so that American patients don't feel compelled to seek alternatives.

FDA is taking a number of other initiatives to improve the regulatory processes to help patients access innovative therapies. Thanks to the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA has agreed to improved review and approval performance metrics tied to dramatic increases in manufacturer user

fees, and we are just beginning to see positive trends in performance. Beyond that, during the last few years, Dr. Shuren and his team at FDA have outlined strategic priorities to strengthen the clinical trial enterprise, striking the right balance between premarket and postmarket data collection and improving customer service.

Over the past year, a number of guidance documents have been drafted to provide manufacturers and FDA reviewers more clarity, including:

- Priority review for premarket submissions
- IDE and IRB approvals
- IDEs for Early Feasibility clinical studies
- Balancing premarket and postmarket data collection
- Expedited access for certain premarket approval devices

In addition, FDA's expanded efforts to improve device quality and safety by shifting the focus from the old regulatory compliance approach to an upfront quality assurance effort through its "Case for Quality" initiative is promising. Finally, FDA's efforts to improve its regulatory management processes and structure through the recommendations coming from its Program Alignment Group are an important step in the right direction. It would be worthwhile for Congress to spend time assessing how we can move this process forward.

It is important to note the distinction of our industry as compared with others in the healthcare space. Whether created by large or small firms, medical technologies are characterized by a rapid innovation cycle. The typical medical device is replaced by an improved version every 18–24 months. To fuel innovation, the medical device industry is research intensive. U.S. medical technology firms spend over twice the U.S. average on research and development.

Research in our industry means that to support regulatory decisions for approval and reimbursement of new medical technologies in the United States, manufacturers are required to gather a great deal of clinical and economic evidence. Evidence development can be an extremely costly endeavor at each stage of the process. Focus should be put on reducing the delay and expense that data collection adds at every step in the process.

FDA has recently proposed a number of improvements to the premarket clinical trial process that hold promise, many of which have already been discussed by the House of Representatives through their 21st Century Cures hearings. Some of these improvements that we support include:

- Streamlining the investigational device exemption (IDE) approval process to reduce IDE approval timeframes.
- Reducing the legal complexity and inconsistency between each hospital Institutional Review Board (IRB) through the creation of a centralized or standardized review process.
- Addressing potentially duplicative clinical evidence through the consideration of surrogate endpoints and greater use of data developed outside of the United States.

In addition to these actions that FDA has already taken, AdvaMed has several proposals that would improve FDA's regulatory processes and support innovation:

- The creation of a "Breakthrough Technology" designation, which would clearly identify which specific and innovative attributes qualify to receive preferential treatment in both the approval and reimbursement process.
- Revitalize the "least burdensome standard" for regulatory review to allow for enhanced reviewer training and the ability for device manufacturers to use valid evidence from alternative sources.
- Encourage FDA to accept international consensus standards.
- Reduce the review burden on FDA and companies by allowing companies to self-certify certain changes to devices if their quality system has been certified as capable of evaluating such changes.
- Streamline the CLIA waiver process to accelerate the availability of point-of-care, rapid diagnostic information to physicians and patients.
- Improve the advisory committee process to reduce delays in product approvals and enhance the fairness and transparency of the process.
- Encourage the development of technologies for rare diseases and pediatric populations.
- Work with FDA to assure that post-market surveillance is effective and efficient; provides timely, reliable, and actionable data; minimizes unnecessary burdens on providers and industry; and is facilitated by smooth implementation of the Unique Device Identifier program.

We look forward to working with the committee and the FDA on these proposals.

WE SHOULD STRENGTHEN THE R&D INFRASTRUCTURE SO THAT IT IS SECOND TO NONE

A robust research and development infrastructure is a critical component of the innovation ecosystem. This committee appreciates the important role that the National Institutes of Health (NIH) plays in advancing science. To continue this work, we support steady growth in funding for the NIH and the National Science Foundation.

Additionally, the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) programs can be improved by raising the amount of funding, allowing larger individual grants to better recognize the costs actually incurred by startup companies.

Last, we can more effectively tap the vast intellectual resources of our Nation's universities and academic health centers by providing Federal technical assistance to establish and diffuse technology transfer best practices.

TO ENCOURAGE INNOVATION, WE NEED TO ADDRESS ISSUES THROUGHOUT THE ENTIRE ECOSYSTEM

It is important to acknowledge that while we take steps to improve the FDA device review process or strengthen the R&D infrastructure, we must also look at the innovation ecosystem as a whole to retain our innovation leadership. There are a few essential elements to fostering an ecosystem that incentivizes curiosity and rewards innovators who develop new therapies for patients:

- Patient/physician need.
- Ready access to capital and supportive economic climate.
- Functional/timely/predictable regulatory processes.
- Reimbursement system that welcomes novel therapies as they undergo a continuous improvement process.
- Strong intellectual property protection.

Unfortunately, however, for the Nation's medical technology industry, every part of the innovation ecosystem is under stress. The danger signs include:

- *Reduced investment*. Venture capital flowing to the medical device sector is both an essential generator of future progress and an index of the attractiveness of investing in the development of new treatments and cures. Venture investment in medical technology declined by 42 percent between 2007 and 2013. First-time funding for medical technology startups dropped by almost three-quarters over the same period.[4]
- *Movement of clinical trials and first product introduction out of the United States*. For more complex products, the new normal is to conduct the first clinical trials and product introductions outside of the United States. Often, patients in other nations get the second or even third version of a novel treatment or diagnostic while patients in the United States are still waiting to get the first version.[5] Among other factors, the decisions to introduce abroad first are driven by the higher cost and time involved in conducting clinical trials in the United States; delays and inconsistencies in FDA review; and, increasingly, uncertainties about coverage and payment. We believe this trend is bad for patients and for American jobs. Where research goes, so goes the high-paying research, engineering and manufacturing jobs. We are encouraged that FDA has made some recent progress in this area through FDA's Early Feasibility Program, which supports the early-stage clinical research. Edwards Lifesciences has been among the fortunate first few companies to benefit from this program through a U.S.-based early feasibility study of a minimally invasive mitral valve replacement technology. We are hopeful the program can be expanded to benefit many other technologies in the future.
- *Increasing difficulty in achieving coverage by public and private insurers for new medical devices and diagnostics*. Start-up companies are now reporting that one of the first questions investors now often ask is about the prospects for coverage and payment, while the previous focus was almost exclusively on the FDA. Public and private insurers have been raising the evidentiary threshold for coverage over the last decade. A new study found that in the 10 years between 2002 and 2012, technologies being considered for national coverage in Medicare were **20 times** less like-

[4] PWC and National Venture Capital Association, "Venture Capital Investments Q1. 2014—Money Tree Results," April, 18, 2014.

[5] California Healthcare Institute and Boston Consulting Group, "Taking the Pulse of Medical Device Regulation and Innovation," 2014.

ly to be successful.[6] When coverage was granted, it was more limited than the FDA approved indications in 40 percent of the cases.[7]

• *Declining U.S. competitiveness*. The U.S. medical technology industry has been the unchallenged world leader for many years. We still lead, but our continued leadership is threatened as other countries are anxious to wrest leadership from the United States. Other countries not only have lower general tax rates but many provide specific tax incentives, such as "patent" or "innovation boxes" designed to further reduce rates for domestic development of intellectual property and manufacturing based on that property, in order to attract high-wage, high value-added knowledge-based manufacturing industries.

• *Shrinking public research infrastructure*. The United States has historically led the world in cutting-edge biomedical research. Public funding of NIH and our great universities and academic health centers has been central to the basic and clinical research that has proven to be the foundation of new treatments and cures. But total U.S.-medical research effort, as a share of global medical research, declined by more than one-fifth in between 2002 and 2012.[8]

I realize that this committee's jurisdiction does not extend to Medicare, but a true innovation agenda must address both FDA and Medicare and I urge this committee and the Senate Finance Committee to consult with each other as you move forward to find ways to promote innovation. One of the most important of our innovation agenda proposals—the breakthrough pathway—spans the jurisdiction of both committees and can only effectively be enacted cooperatively.

THE PATIENT EXPERIENCE

No discussion about medical technology is complete without understanding the true impact medical advancements have on patients—and we meet a lot of patients.

Earlier this month, we had the pleasure of hosting 50 patients who participated in our first ever Edwards Patient Day held at our Irvine, CA headquarters. We brought them there to connect with one another, and to meet the dedicated team of employees who hand-sew every heart valve, stitch by careful stitch. Needless to say, it was a very emotional day for the patients as well as the teams who created their lifesaving valve.

During Patient Day, we met a woman from Colorado who survived Hodgkins lymphoma, but found out she needed a heart valve replacement due to severe aortic stenosis. Since her doctors were not about to crack open her chest made frail by radiation, she was a candidate to receive a transcatheter valve replacement. She told us how her new valve has kept her healthy and allowed her to get back to her life as a middle school teacher.

We also met a Marine Corps veteran who received TAVR treatment at the VA in Ann Arbor, and was discharged only 48 hours after his procedure. His valve was replaced in January, completely recovered, making the trip from Michigan to Irvine a few weeks ago to share his story with other veterans and Patient Day participants.

It is patients like these—a Salt Lake City father of 10 and grandfather to 25 who received a valve replacement as part of a clinical trial studying the next-generation treatment, and a New York marathoner who, after heart valve replacement, was able to return to running—that remind us of the importance of our daily work, and the chance to bring our ideas out of the lab, into the clinic and to the patients and physicians that need them most.

These and the tens of thousands of other patients we have had an opportunity to help remind us daily that our work is personal, and it impacts people individually. Each heart valve represents a patient and their family, who otherwise would miss out on both the extraordinary and precious ordinary experiences of their daily lives.

Our mission is focused and our way forward is clear. I thank Chairman Alexander, Ranking Member Murray and members of the committee for the opportunity to testify today, and to share Edwards' experience in delivering an important new therapy to U.S. patients in need. We look forward to continuing to work with you to support the U.S. innovation ecosystem.

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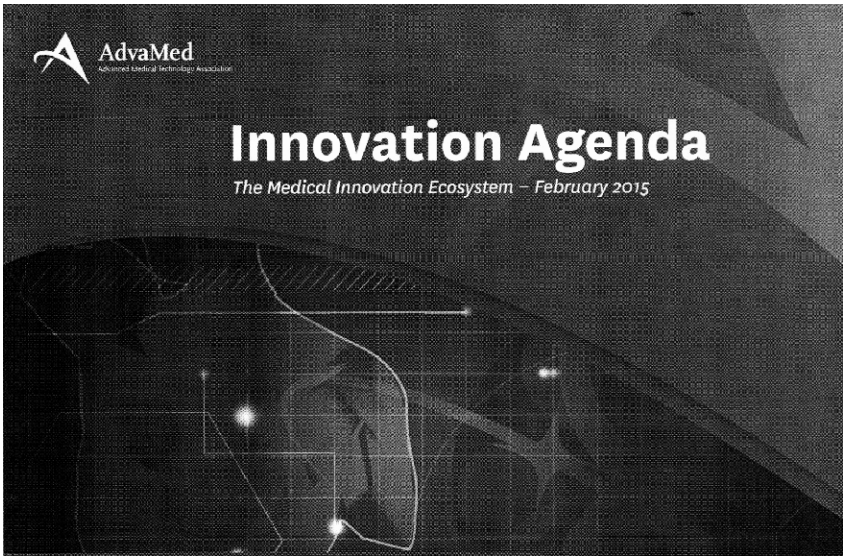
[6] James D. Chambers, et al., "Medicare is Scrutinizing Evidence More Tightly for National Coverage Determinations," Health Affairs, February 2015.

[7] James D. Chambers, et al., "Factors Predicting Medicare National Coverage: an Empirical Analysis," Medical Care, March 2012.

[8] Hamilton Moses, III, M.D., et al., "The Anatomy of Medical Research: U.S. and International Comparisons," JAMA, 2015;313(2): 174–189.

Attachment



INNOVATION AGENDA BACKGROUND

The medical technology industry is central to the development of medical devices and diagnostics that will provide the life-saving and life-enhancing treatments of the future. Patient access to advanced medical technology generates efficiencies and cost savings for the health care system, and improves the quality of patient care. Between 1980 and 2010, advanced medical technology helped cut the number of days people spent in hospitals by more than half and add 5 years to U.S. life expectancy while reducing fatalities from heart disease and stroke by more than half. The industry is also an engine of economic growth for the United States, generating high wage manufacturing jobs and a favorable balance of payments.

But the innovation ecosystem that supports medical technology is severely stressed. The United States has historically been the world leader in medical technology, but our leadership is eroding. Venture capital investment, especially investment in the startup firms that are the seed corn of the industry, has plummeted. While there have been recent improvements at the FDA, the regulatory process remains too time-consuming, too inefficient, and too inconsistent. The payment environment is far less hospitable to new technology today than ever before, with the result that investment in new treatments is discouraged and patient access to new treatments that are developed is slower and more difficult. The U.S. tax system is uncompetitive and discourages location of research and development and manufacturing in the United States, a situation that has dramatically worsened as the result of the medical device excise tax. The basic and applied public infrastructure that is critical to long-term advances in the life sciences is eroding.

To respond to these challenges and rebuild the innovation ecosystem, AdvaMed proposes a new Innovation Agenda. Enactment of this agenda will unleash the potential of medical technology to extend and improve lives, reduce the cost and burden of disease, and maintain and enhance U.S. scientific and economic leadership. Failure to act will mean lost lives, unnecessary suffering, reduced job formation, and diminished economic growth.

The Five Pillars of the Innovation Agenda

1	2	3	4	5
Improving FDA's regulatory processes so that the cost and time of development and approval of devices and diagnostics is reduced and the CDRH mission statement that American patients will be the first in the world to have access to new devices is achieved, while maintaining the highest standards of safety and efficacy.	**Restructuring CMS's coverage and payment processes** to support development of new technologies that improve treatment, diagnosis or prevention, and provide prompt patient access to these technologies.	**Reform the U.S. tax system to create a level playing field,** starting with repeal of the medical device excise tax—a tax that is draining resources from American manufacturing jobs and research.	**Improving access to international markets** by insisting on free and fair trade in medical technology and working with foreign governments to achieve innovation-friendly regulatory and payment policies.	**Supporting the maintenance and growth of an R&D infrastructure** second to none.

PROPOSALS TO IMPLEMENT THE INNOVATION AGENDA

Establish access to breakthrough products

• Establish a streamlined, seamless path for FDA approval and CMS coverage and payment under the Medicare and Medicaid programs for breakthrough products that make significant improvements in treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

Improve the FDA's regulatory processes

Responding to patient challenges and to rebuild the innovation ecosystem, AdvaMed proposes a new Innovation Agenda.

• Meet and exceed the groundbreaking 2012 user-fee agreement goals for such key objectives as reductions in total review times and more frequent and substantive interactions between FDA and product sponsors.
• Revitalize the "least burdensome standard" for regulatory review through enhanced reviewer training and encouraging the use of valid scientific evidence from such sources as registries, experience in foreign markets, and peer-reviewed journal articles, where appropriate, to support safety or effectiveness determinations.
• Encourage FDA to accept international consensus standards.
• Streamline the CLIA waiver process to accelerate the availability of point-of-care, rapid diagnostic information to physicians and patients.
• Allow the use of central Institutional Review Boards to facilitate the conduct of multicenter clinical trials.
• Reduce the review burden on FDA and companies by allowing companies to self-certify minor changes to devices if their quality system has been certified as capable of evaluating such changes.
• Improve the advisory committee process to reduce delays in product approvals and enhance the fairness and transparency of the process.
• Encourage the development of technologies for rare diseases and pediatric populations.
• Work with FDA to assure that post-market surveillance is effective and efficient; provides timely, reliable, and actionable data; minimizes unnecessary burdens on providers and industry; and is facilitated by smooth implementation of the Unique Device Identifier program.

Restructure CMS's coverage and payment processes

Enactment of AdvaMed's Innovation Agenda will unleash the potential of medical technology to improve lives, reduce the cost and burden of disease, and enhance U.S. scientific and economic leadership.

• Establish automatic Medicare coverage of FDA-approved clinical trials rather than requiring a duplicative and potentially time-consuming separate Medicare approval process.
• Expand coverage of telehealth services, including remote monitoring, and of disposable, prevention and treatment technologies used in the home.
• Streamline Medicare's process for granting temporary outpatient and physician payment codes to new technologies and prohibit Medicare contractors from arbitrarily denying payment for these technologies.

• Require State Medicaid programs to take patient views into account in making coverage decisions.
• Increase the transparency and fairness of the local coverage determination process.
• Improve the new technology add-on payment program to capture a larger share of important new technologies and set payments more appropriately.
• Establish payment levels more promptly for new technologies used in the inpatient setting, using the best available data.
• Improve the methodology for establishing payment for technologies used in the outpatient setting and for updating payments to ambulatory surgical centers.
• Implement ICD–10 this fiscal year.

Reform the U.S. tax system

• Repeal the medical device excise tax.
• In the context of comprehensive tax reform, create a level competitive playing field for made-in-America medical technology:
  • Enact new tax incentives to invest in startup companies creating new treatments and diagnostics;
  • Lower the overall corporate tax rate;
  • Provide incentives comparable to those of other countries for development and manufacturing of technology; and
  • Conform the treatment of international earnings to that of competitor nations.

Improve access to international markets

• Work with the U.S. Government to encourage foreign governments to establish regulatory and payment systems for medical technology that are fair, transparent, nondiscriminatory and based on international best practices.
• Enact Trade Promotion Authority to negotiate the Trans-Pacific Partnership and the Trans-Atlantic Trade and Investment Partnership, and assure that those agreements include provisions that improve market access for medical technology.
• Enforce provisions of existing trade agreements such as the U.S.-Korea Free Trade Agreement to assure fair access for U.S. technology products.

Support the maintenance and growth of an R&D infrastructure second to none

The medical technology industry is central to the development of medical devices and diagnostics that provide life-saving and life-enhancing treatments of the future.

• Provide steady growth in funding for the National Institutes of Health and the National Science Foundation.
• Improve the Small Business Innovation Research and Small Business Technology Transfer programs by raising the amount of funding (in the context of rising NIH and NSF funding), allowing larger individual grants to better recognize the costs actually incurred by startup companies.
• More effectively tap the vast intellectual resources of our Nation's universities and academic health centers by providing Federal technical assistance to establish and diffuse technology transfer best practices.
• Streamline Institutional Review Board activities to reduce barriers to initiating collection of clinical data on new treatments, particularly for multicenter trials, without sacrificing protection of human subjects.

The CHAIRMAN. Thank you, Mr. Mussallem.

Mr. Coukell.

STATEMENT OF ALLAN COUKELL, SENIOR DIRECTOR, HEALTH PROGRAMS, PEW CHARITABLE TRUSTS, WASHINGTON, DC

Mr. COUKELL. Chairman Alexander, Ranking Member Murray, and members of the committee, thank you for the opportunity to be here. My name is Allan Coukell. I direct health programs at the Pew Charitable Trusts. We're an independent, nonpartisan research and policy organization that operates a number of drug and medical device initiatives.

My testimony today makes three main points. First, the rising cost of medical innovation is a serious concern with multiple underlying causes. Second, the FDA has great flexibility but would benefit from additional tools in some areas. And, third, the need for

robust clinical data is higher than ever, and there are steps Congress could take to improve the efficiency of data collection.

We live in a time of exciting scientific and therapeutic advances, and yet the cost of bringing drugs to market has risen steadily. To give just one fact, the per-patient cost of clinical trials jumped 86 percent over 3 years, by one recent estimate.

Numerous reviews and analyses have shown that the regulatory environment is not the sole or even the main cause of declining industry productivity. Nevertheless, it's imperative that FDA regulation and the other public programs that support innovation work as efficiently as possible.

Yet we must recognize the challenge. For many drugs and devices, the clinical effects are subtle. Unless you study a lot of patients, using carefully controlled experiments to reduce accidental bias, you can't necessarily tell if they work. The crucial point is that the size of clinical trials is driven not by the approval standard written into the law, but by the difficulty of discerning the effect of treatment.

To my second point about FDA flexibility, there is no one-size-fits-all requirement for evidence to support drug or device approval. Drugs can be and are approved based on a single trial about a third of the time, using historical controls and so on as suited to that product.

Congress has created a variety of pathways to speed approvals. For example, 20 percent of novel new drugs last year came to market through accelerated approval based on surrogate outcomes. Now, a similar approach has been proposed for medical devices, FDA's expedited access PMA pathway. If Congress codifies this program, it should ensure that FDA also has the ability to remove devices that ultimately are not found to be safe and effective.

These various mechanisms are especially important for products that advance care for patients with serious unmet needs. One area where Congress could facilitate innovation is the development of a new regulatory pathway for antibiotics. Senators Hatch and Bennet have introduced the PATH Act which would direct FDA to approve drugs for specific limited populations of patients who have life-threatening infections and few other treatment options or none.

Such resistant infections are on the rise and threaten to become a public health crisis. A number of key stakeholders, including public health groups, providers, industry, and venture capital, support this legislation. Pew asks the committee to move it quickly and to limit the pathway to antibiotics.

Let me now turn to my third point, the efficiency of clinical data collection. My written testimony contains a number of suggestions, but let me focus here on the potential for far-reaching change. I'll give you an example of the kind of study that we should be conducting in the United States but right now can't, at least not routinely.

A few years ago, investigators in Scandinavia randomized 7,000 patients to two different surgical treatments for blocked coronary vessels. A traditional trial like this in the United States would cost hundreds of millions of dollars. This one in Europe cost $300,000, $50 per patient.

Why was it so cheap? Because the data for the trial were drawn from a cardiovascular disease registry, a database that collects information on groups of patients treated for a given condition. Registries have been used to a limited extent in the United States, and Mr. Mussallem mentioned that his product, an innovative heart valve, got an expanded indication based on registry data in lieu of a clinical trial.

Pew worked with a range of stakeholders to develop a report on what it would take to make registries cheaper and more common in the United States. We found that one of the major barriers is the lack of electronic health record interoperability. Another is legal confusion between research and quality improvement. Finally, there's the need for a sustainable funding model.

Addressing these challenges could put us on a footing to reduce the cost of innovation, speed approvals, and make better decisions about performance and cost once the product is on the market.

In conclusion, Mr. Chairman, medical product innovation involves partnerships across the private sector, basic science and academia, the regulatory environment, and the public programs that pay for new technology. We should continue to improve the system, recognizing that each part has its role to play and that patients rely on it.

Thank you, and I'd welcome any questions.

[The prepared statement of Mr. Coukell follows:]

PREPARED STATEMENT OF ALLAN COUKELL

SUMMARY

In addition to touching briefly on FDA operations, my testimony makes three key points:

- The rising cost of medical product innovation is a serious concern, with multiple underlying causes.
- The FDA has great flexibility, but would benefit from additional tools in some areas.
- The need for robust clinical data is higher than ever, and there are steps Congress could take to improve the efficiency of data collection.

Since 1950, the Food and Drug Administration (FDA) has approved more than 1,400 drugs, at a relatively constant annual rate. Numerous recent approvals demonstrate scientific novelty and exciting therapeutic potential. However, the inflation-adjusted cost of bringing these products to market has risen steadily. As numerous reviews and analyses have shown, the regulatory environment is not the sole, nor even the principal, cause of this declining productivity.

Nevertheless, it is imperative that FDA regulation and other public programs that support innovation work as efficiently as possible. Patients, clinicians, and product developers rely on the FDA's careful and efficient review of new products.

There is no "one-size-fits-all" requirement for evidence to support drug or device approval. FDA's drug and device centers have, and routinely use, flexibility in approving new products, including use of a variety of pathways and mechanisms created by Congress.

One proposed new pathway—the expedited access premarket approval (EAP) process for medical devices—would support the marketing of new medical devices based on surrogate endpoints, shorter clinical trials or other adaptive designs, but its enactment should include mechanisms to ensure that sufficient data is collected in the post-market setting and that devices do not remain on the market absent such data.

Another area where Congress could facilitate innovation is the development of a new regulatory pathway for FDA to approve new antibiotics for specific, limited populations of patients with life-threatening infections where few or no treatment options currently exist.

Senators Hatch and Bennet have introduced the PATH Act, S. 185, which would direct FDA to create this pathway for antibiotics. A number of key stakeholders, in-

cluding public health groups, providers, industry, and venture capital, support this legislation and we ask the committee to move this bill quickly.

To facilitate more efficient innovation and better evaluation of product performance in the pre- and post-market setting, it is important to address the rising cost of clinical trials and clinical data acquisition. Clinical trials remain the most reliable source of unbiased information for evaluating clinical effectiveness and Congress could help address these costs by facilitating faster trial initiation through, for example, greater use of central institutional review boards (IRBs). More far-reaching reforms would increase the use of clinical registries (databases) as a source of clinical data.

While sponsors have concerns about the speed and predictability of FDA review, they generally feel that requests for data are appropriate and the agency makes the correct decision in most cases. There is general support for increased investment in FDA training and personnel and in regulatory science.

Chairman Alexander, Ranking Member Murray, and members of the committee. My name is Allan Coukell. I direct health programs at The Pew Charitable Trusts, an independent, non-partisan research and policy organization with a number of initiatives focused on drug and medical device safety and innovation.

Thank you for the opportunity to present testimony on the medical product development landscape. I will focus today on steps that could support innovation, with a particular emphasis on the need for robust clinical data to evaluate product performance both before and after approval. I will touch, in particular, on drug approvals and Pew's medical device and antibiotic innovation work, as well as on FDA predictability.

In addition to touching briefly on FDA operations, my testimony makes three key points:

- The rising cost of medical product innovation is a serious concern, with multiple underlying causes.
- The FDA has great flexibility, but would benefit from additional tools in some areas.
- The need for robust clinical data is higher than ever, and there are steps Congress could take to improve the efficiency of data collection.

Since 1950, the Food and Drug Administration (FDA) has approved more than 1,400 drugs. Aside from an increase in approvals after the enactment of the first Prescription Drug User Fee Act (PDUFA), the number of annual approvals has been relatively constant over this period,[1] while the inflation-adjusted cost of bringing these products to market has risen steadily. As numerous reviews and analyses have shown, the regulatory environment is not the sole, nor even the principal, cause of this declining productivity.[1 2 3]

Nevertheless, it is imperative that FDA regulation and other public programs that support innovation work as efficiently as possible. Patients, clinicians, and product developers rely on the FDA's careful and efficient review of new products.

Pharmaceutical research and development investment in the United States has remained flat over the past decade, while investments in medical device and biotechnology, though much smaller, have grown steadily.[4] The United States continues to lead the world in many aspects of biomedical innovation,[4 5 6] and recent scientific and clinical advances are encouraging; however, there are very real strains in the business models for both drug and medical device development—and in our ability to manage the associated costs of these products.

FDA APPROVALS AND FLEXIBILITY

In approving new drugs, FDA relies on a "substantial evidence of effectiveness" standard established by "adequate and well-controlled investigations, including clinical investigations." The medical device standard is similar: "reasonable assurance of safety and effectiveness" based on "valid scientific evidence."

There is no "one-size-fits-all" requirement for evidence to support drug or device approval. For example, an analysis by the National Organization for Rare Disorders found that of 135 drug approvals for non-cancer rare disease, 45 met traditional data requirements, 32 reflected "administrative flexibility" based on a previously documented FDA system, and 58 reflected flexibility applied on a case-by-case basis.[7] Another recent analysis of all drug approvals (funded by Pew) found that while FDA generally relied on randomized clinical trials to approve therapeutics, over one-third of approvals were based on a single efficacy trial.[8] This same analysis also showed that FDA used flexibility with regards to which outcomes these trials had to measure.

FDA's review of safety and effectiveness data is essential to inform patients and physicians. For many drugs and devices, the clinical effects are difficult to distinguish from the normal variation in outcomes seen in the relevant population of patients. Often, a drug's effect can only be assessed across large numbers of patients through careful experiments designed to reduce confounding and accidental bias. The crucial point is that the size of clinical trials is driven, *not by the approval standard written in statute*, but by the difficulty of discerning the effect of the treatment.

It is important to note that early promise for drugs and devices may not be borne out as the products proceed through development. A recent Pew study found that even among medical devices that the FDA had identified as sufficiently innovative to qualify for priority review status, approximately one-third were not ultimately approved.[9] This shows, again, that novelty and early promise are not always borne out by more thorough testing.

Several existing mechanisms provide flexibility for the data collected. The accelerated approval pathway for drugs, which Congress codified into law in 2012, allows FDA approval based on surrogate—rather than clinical—endpoints, with the goal of enabling more efficient premarket studies. In 2014, FDA approved 20 percent of novel new drugs through this pathway.[10]

Similarly, for devices that treat or diagnose conditions affecting fewer than 4,000 patients per year, FDA can grant a humanitarian device exemption, which allows the marketing of a product that is considered safe and is expected to provide benefits, even if less evidence on effectiveness is available. The FDA's proposed expedited access premarket approval (EAP) process for medical devices would also support the marketing of new medical devices based on surrogate endpoints, shorter clinical trials or other adaptive designs. The success of this policy, though, relies on the efficient collection of data—both pre- and post-market. Congress should explore codifying this program in statute, and should address some gaps in FDA's authority to accelerate patient access to new medical devices while still collecting sufficient information throughout a product's entire life cycle. In particular, Congress should assess the agency's ability to promptly remove the approval of devices that ultimately were not found to be safe and effective.[11]

These programs provide FDA with significant latitude to tailor the data collected by sponsors and the agency's review process to reflect the severity of the disease and availability of alternative treatments, not to mention each product's risks and benefits.

Limited Population Antibacterial Drug Approvals

One area where Congress could facilitate innovation is the development of a new regulatory pathway for FDA to approve new antibiotics for specific, limited populations of patients with life-threatening infections where few or no treatment options currently exist.[12] We have an urgent need for new antibiotics. Antibiotic resistance is rising and there are increasing infections for which we have almost no treatments. Currently, for the FDA to approve a new antibiotic the FDA generally requires extensive clinical trials in the larger population due to concerns about safety risks resulting from possible use in broader groups. It would be desirable to have a pathway—twice endorsed by the President's Council of Advisors on Science and Technology (PCAST)[13]—under which such drugs could rapidly reach high-need patients while reducing the risks from wider use of the drug. There would also be clear public health benefits to limiting the use of new antibiotics effective against drug-resistant bacteria, to stave off the emergence of drug-resistant strains.

Senators Hatch and Bennet have introduced the PATH Act, S. 185, which would direct FDA to create this pathway for antibiotics. A number of key stakeholders, including public health groups, providers, industry, and venture capital, support this legislation, and we ask the committee to move this bill quickly.

Patients May Need More Evidence

It is important to note that current approval standards speak only to efficacy and safety. Stakeholders beyond the FDA—notably patients and payors—may frequently need additional information to make informed choices. For a patient, the question may not be whether a drug is effective compared with a placebo, but whether it is superior to other existing treatments. Patients and payors alike may seek to evaluate that information and weigh it against the drug's cost. These are crucial questions for the individual that are not addressed by the current approval standard. In addition, drug costs—particularly for high-cost biologics that make up an increasing share of drug approvals—are rising faster than healthcare costs as a whole. The need to sustainably mange health-care spending is likely to drive further demands for data to assess the value of new drugs and treatments, and not merely their effec-

tiveness.[14] For example, one of the Nation's leading cancer centers recently announced that it would not utilize a particular new cancer drug because the drug was more expensive than its competitors, but did not confer additional benefit.[15]

BETTER DATA AT LOWER COST

To facilitate more efficient collection of evidence in both the pre-market and post-market setting, it is important to address the rising cost of clinical trials and clinical data acquisition. Clinical trials remain the most reliable source of unbiased information for evaluating clinical effectiveness,[16] and Congress could help address these costs by facilitating faster trial initiation through, for example, greater use of central institutional review boards (IRBs) instead of multiple local reviews. For medical devices in particular, trials are currently required by statute to obtain IRB review at each facility participating in a study.[17] Removing this requirement could help streamline the approval of these trials.

Personalized, or precision, medicine has the potential to identify sub-populations of patients with specific genetic profiles who are more likely to respond to a particular therapy—particularly in cancer treatment. To take full advantage of this potential will require innovative trial designs, which the FDA has encouraged. For example, the recently developed Lung-MAP trial has the potential to improve efficiency by allowing simultaneous and sequential comparisons of multiple drugs (from multiple companies) and stratification of patients by genotype.[18]

Per Patient Costs and Large Simple Trials

Independent of the size of the trial, per-patient clinical trial costs have risen sharply. A 2013 survey found that phase III costs rose by 86 to 88 percent over 3 years (from $25,000 to $40,000 per patient).[19] Across all development phases, the increase was 70 percent. The report notes that finding a sufficient number of general clinical sites is a challenge, but that,

> "The biggest driver behind higher vendor costs and site recruitment issues is an increasingly intense competition for top-performing investigator sites."

One source of cost in any trial is the number of data elements that are collected. Another approach to reducing trial costs involves "large, simple trials."[20] Such trials have the potential to reduce costs by simplifying eligibility criteria and reducing the number of outcomes tracked. No statutory or regulatory barrier precludes adoption of such trial designs. Rather, a participant in an IOM workshop described the barrier as risk aversion, with researchers preferring to collect 100 unnecessary variables than to miss one important one.[20]

Registries

One successful large simple trial randomized patients through use of an existing cardiovascular disease registry in Sweden. Registries are large databases that collect information on groups of patients treated for a particular medical condition. The TASTE trial enrolled more than 7,000 patients, and—in unprecedented fashion—allowed investigators to keep track of every patient throughout the course of the research at a total cost of $50 per patient, or only $300,000 for the entire trial.[21] Conducting a traditional study of this size in the United States would cost hundreds of millions of dollars, if not more.

Registries have been used to a limited extent in the United States to expedite patient access to new products. Notably, the FDA has approved an expanded indication for an innovative heart valve based on data from an existing registry, in lieu of a randomized clinical trial. Pew, together with the Blue Cross Blue Shield Association and the Medical Device Epidemiology Network, convened experts from the medical device industry, the registry community and government to consider how to achieve the full potential of registries in a financially sustainable way.[22]

Several barriers exist to fully achieving the promise of registries. Despite the dramatic uptake of electronic health information sources, these systems cannot easily transmit data among one another. This lack of interoperability, for example, hinders the ability of registries to extract clinical and outcomes data from EHRs. Instead, registries must develop the ability to extract information from the EHR systems at each facility, or require manual entry from providers. Additionally, many registries have sought clarity on when their studies are considered research, rather than quality improvement efforts. This confusion has slowed their use by hospitals and their ability to make a meaningful contribution.

Post-market Data and Expedited Device Approval

Better post-market data—from registries and other sources—would facilitate more effective FDA regulation across the total product life cycle. For example, FDA has proposed an expedited access premarket approval policy for devices that fill serious,

unmet medical needs. Under this program, FDA would implement a total-product-life-cycle approach to regulation by accepting more uncertainty on some of the effects of new products and require the answers to those questions from post-market studies. As a result, FDA could accept smaller trials and the use of surrogate endpoints or short followup on patients in the premarket setting, with additional data collected after approval. This approach—so long as it remains tailored to only those devices that will significantly improve the options available for patients with serious conditions—can help reduce the time to market of new products without sacrificing the data collected on the products.

"REAL WORLD" AND POST-MARKET DATA

As FDA continues to implement a total-product-life-cycle approach to regulation, better post-market controls and data can provide assurances that any problems not detected by clinical trials are promptly identified after approval. The FDA may be reluctant to approve products more quickly if the agency is not confident that safety problems will be detected in the post-market setting. At present, the ability to assess product performance based on claims, electronic health record and registry data is extremely limited (see, for example, Madigan *et al*.'s description of varying results depending on the choice of database).[23]

As previously stated, developing the infrastructure to more efficiently collect and evaluate such information could substantially reduce the long-term cost of acquiring clinical data. It may also allow for evaluation of products across a wider range of conditions and patient populations. However, it is important to note that building this capacity will require investment in both infrastructure and methods development.

Along with the use of registries to gather this information, systems such as the FDA's post-market surveillance Sentinel Initiative can provide better longitudinal data on product performance. Sentinel, a distributed database that includes data from 178 million individuals, illustrates the potential of real world evidence, but also its challenges.[24] The FDA already uses Sentinel to evaluate drug safety, and Congress instructed the agency to expand this initiative to devices. However, the Sentinel program relies primarily on claims data, which lack information on the specific device used in care. If integrated into claims, the new unique device identifier (UDI) system can provide that specificity by clearly indicating the manufacturer and model of the device used. The Centers for Medicare & Medicaid Services must issue regulations to update the claims form to include this information so that FDA can utilize Sentinel—in accordance with the congressional directive—to evaluate device safety.

In addition, a report released last month from a multi-stakeholder group of medical device safety experts recommended several reforms and investments to support more robust data on the performance of new technologies after approval. For example, the National Medical Device Post-market Surveillance System Planning Board endorsed the inclusion of documenting UDI in claims to develop better data on the long-term performance of medical devices. In addition, the Planning Board recommended the development of a public-private partnership to advance, oversee and coordinate efforts to evaluate the quality of marketed devices. Congress should evaluate the Planning Board proposal and encourage all stakeholders—including FDA, CMS, manufacturers, clinicians and health plans—to develop a more robust post-market surveillance infrastructure.

SYSTEMIC FDA CHALLENGES

FDA's most important resource is its staff, including physicians, statisticians, scientists and biomedical engineers that review medical product applications, data from clinical trials and post-market information.

A 2012 Pew-funded report from the Partnership for Public Service (PPS) found several challenges to FDA's hiring, recruitment and retention of these scientific and medical experts. PPS recommended that FDA develop targeted recruitment programs to fill its talent pipeline, invest in career training and leadership development programs, and implement strategies to reduce attrition rates.[25]

Perhaps the most commonly cited measure of FDA performance is drug approval time. Recent studies have demonstrated that FDA approves drugs more quickly than regulators in Europe and Canada.[8] [26] Moreover, median time to approval today is substantially lower than prior to the implementation of PDUFA goals.[27] Over recent decades, the overall success rate for New Drug Applications (NDAs) has been relatively consistent (averaging 79 percent from 1993–2012), but the share of drugs approved at the first action date has increased markedly (45 percent over 20 years, but 77 percent in 2011–12).[28] To a large extent that is a function of the quality of

the applications.[29] FDA has some capacity to influence submission quality through its communication with industry, either during individual meetings or through guidance documents. According to a recent PwC survey of industry executives, 78 percent responded that FDA has improved the quality and frequency of its communications with industry over the last 2 years, and 76 percent responded that the agency provided "actionable feedback."[30]

Successive FDA user-fee agreements have provided the agency with resources to facilitate the evaluation of medical products and have established new FDA performance metrics and formal mechanisms for interaction between the FDA and sponsors. Nevertheless, a frequently cited barrier to medical product development is an absence of predictability in the FDA's regulatory review processes.[31 32 33 34] As part of negotiations to reauthorize the prescription drug and medical device user fees through the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), both industries highlighted improving regulatory predictability as a major goal and, in the case of devices, a "paramount" concern.[35 36]

Regulatory predictability may be defined as agency decisions that are not arbitrary, arrived at through transparent procedures, consistently enforced, and free of bias.[37] However, discussions about regulatory predictability frequently lack specificity. Efforts to assess or improve predictability may be confounded by the complex scientific and regulatory environment in which drug and device regulation occurs. Moreover, this environment is not static; no two products are exactly alike, and the understanding of disease changes and improves over time, as does the science of evaluating product performance. And science itself is unpredictable: the act of evaluating a product may generate information that raises further questions or undermines confidence in the outcome of a study, thus requiring further investigation. Fundamentally, regulatory decisions involve value judgments about the acceptable level of uncertainty in the data used to assess both safety and efficacy.

An upcoming Pew report summarizes the results of an industry survey and expert conference with industry and FDA leaders on predictability. The survey showed concern about FDA processes and timing, but found that a large majority agrees with FDA's ultimate decisions—saying the FDA makes the appropriate decision on new medical products "most or all of the time." In addition, about 62 percent of the respondents said FDA's data requirements are necessary in "all or more cases," with only 2 percent saying the requirements were necessary in "very few cases."

When probed further, most respondents to the survey as well as workshop participants expressed concerns regarding the agency's predictability. Thirty-eight percent of industry respondents said, based on their personal experiences, that the FDA's regulatory review process is "completely or fairly" predictable (higher among biotechnology and pharmaceutical professionals and lower among medical device professionals). The discrepancy among drug versus device executives was a consistent pattern, perhaps attributable to the greater diversity of medical devices products and companies and the breadth of approaches to testing their safety and efficacy, as well as staffing issues within CDRH, which the division acknowledged.

Overall, 68 percent of respondents said that such unpredictability discouraged the development of new products. A third (36 percent) said the agency strikes the right balance between speed and safety. Industry professionals were divided on the degree to which they believed the system needs to be fixed. Nearly half (49 percent) believe the agency's product review systems need a "complete or major overhaul." The same number said the systems worked "fine as-is" or needed only "minor modifications."

It is important to recognize that regulatory predictability is a broad and subjective term used to describe a variety of issues. Therefore, attempts to solve "regulatory predictability" are less likely to succeed because the problem itself is not defined precisely enough. Rather than relying on this broad diagnosis, stakeholders would be better served to articulate issues regarding, for example, communications, staff experience, or data accessibility.

To aid in that process, we briefly characterize several of these commonly cited facets of unpredictability and potential solutions to address them. These proposals reflect ideas raised by sponsors, FDA officials, analysts, researchers, and other stakeholders during the course of our research:

- Establishing clear data requirements;
- Inconsistency among FDA reviewers and review divisions;
- Issues related to the publication of guidances;
- Data integration and accessibility; and
- Sponsor inexperience with regulatory review.

Sponsors sometimes assert that there is often a lack of clarity or explicit rationale regarding the type and quantity of additional safety and efficacy data that FDA staff requests. Specifically, several sponsors asserted that such requests are mani-

festations of an inherent and unwarranted "risk-aversion" on the part of FDA staff. Sponsors assert that some officials lack an understanding about how much risk the agency is willing to tolerate. As they submit documents to the agency, FDA staff will request additional information to address possible concerns with a product or learn more about how a drug will affect patients. Sponsors contend that many of these data requests would negligibly affect FDA's decisions but are burdensome and expensive. Similarly, they assert that some data requests are too academic and not germane to the safety and efficacy of a product.

Current and former FDA officials we spoke with contend that the FDA must maintain some measure of flexibility when evaluating sponsors' applications. Over the course of a product's lifecycle new information may become available—from the scientific literature, from its regulatory counterparts in other jurisdictions, among other places—that compels the FDA to look at a sponsor's application in a new light. Moreover, in the course of reviewing applications from other sponsors on a similar product, and through post-marketing surveillance monitoring, FDA reviewers identify potential safety and efficacy issues with a product class and uses that information to make additional data requests of sponsors. Because specific reference to other sponsor's applications is prohibited by commercial confidentiality laws, FDA staff cannot always be specific about the reasons underlying a particular data request, leading to sponsor perceptions of FDA capriciousness or arbitrariness.

To achieve greater predictability, our conference found substantial support for the suggestion that the FDA should release all documents—such as Complete Response Letters—that provide information on why the agency requested additional information or declined to approve a product. (Complete Response letters are effectively the FDA's communication to a sponsor of why a product is not approved; currently the FDA does not release these letters publicly.) That information will help all companies understand the data sought for certain diseases and about classes of medical products.

Most respondents (78 percent) suggested that investing in human resources, such as training staff, would be a "fairly" or "very" effective strategy for improving FDA's review process, making this the most popular proposal offered in the survey.

The FDA's centers for drugs and devices both have established a number of programs and pathways that facilitate earlier and more frequent interactions between sponsors and agency staff. When meeting with the FDA about adaptive trial designs or other issues that are not typical for a standard drug application, sponsors should request the attendance and input of senior FDA leadership. Such input could provide needed reassurance to reviewers and assuage their concerns with a product review.

Inexperience submitting products for FDA review leads to sponsors maintaining inaccurate expectations about data requirements and agency processes, ultimately resulting in perceptions of unpredictability when those expectations are not met. Small companies are especially susceptible to this problem. A study by Booz Allen Hamilton found that large companies obtain approval on their original submission 58 percent of the time, whereas that is true for only 41 percent of small company submissions.[29] More recently, a PriceWaterhouseCoopers survey found that large companies were more likely to avail themselves of interactions with the FDA; smaller companies were more likely to rely on guidance.[30]

Sponsors that have not previously submitted products to the FDA for review may lack an accurate understanding of the data requirements and agency processes. Moreover, many small companies fail to hire experienced consultants and regulatory experts to assist with product submissions. Without this help, companies may submit inadequate or noncompliant submissions to the FDA.

Other measures provide insights on additional aspects of agency operations, such as presentations to societies, consortia, industry and government organizations (around 100 per month for the center for drugs).[38] Of particular interest may be issuance of FDA guidance documents, which serve to communicate the agency's current thinking on specific topics. The center for drugs, for example, issued 51 draft guidances in 2014, but only 13 final guidances.[39] Earlier years follow a similar pattern. The reasons for this discrepancy are unclear. It may be that the agency seeks a wide range of input during development of a draft guidance, which then serves as an effective tool for communicating with stakeholders. Alternatively, it may be that the process for administrative clearance deters the agency from finalizing guidances. Congress could evaluate the balance between finalizing guidances and the potential opportunity cost of fewer new draft guidances on other topics, and potentially identify administrative simplifications that would facilitate finalization. A similar investigation of the time required to develop and finalize a formal FDA rule (often several years) might lead to solutions that would support greater overall efficiency.

REGULATORY SCIENCE AND PUBLIC PRIVATE PARTNERSHIPS

FDA has focused on the need for better tools to inform its decisionmaking at least since the Critical Path report in 2004, and more recently through its Regulatory Science strategic plan and associated initiatives.[40] The regulatory science rubric is used by the agency and stakeholders to refer both to the development of tools and approaches for use by sponsors and to the development of approaches the agency may use in decisionmaking.

Pew's predictability survey found strong support for investment in regulatory science as a "very or fairly effective" means to improve the review process.

Mittleman *et al*.[41] provide an excellent overview of the opportunities for precompetitive consortia, noting both their potential and the need for more investment. They find that these organizations succeed by bringing together industry, academics, government and mission-driven non-profits to deliver on separate and shared interests. However, these organizations require time and resources to produce results. For example, the Biomarkers Consortium took nearly 2 years of negotiations to bridge the divergent standards and practices, including IP considerations, of various stakeholders. That organization has now initiated 15 projects, with its first completed in 2009. In contrast with the $2.7 billion European investment in the Innovative Medicines Initiative, U.S. support of the various consortia has been limited.

While universities and government are not configured to develop medicines, public-private partnerships have the potential to spur innovation. For example, Pew's focus on antibiotic development has shown that there are key scientific questions that could underpin a resurgence in antibiotic discovery, but are currently the province of neither industry nor academia. One barrier to progress, or at least to efficient progress, is that academic scientists may not have complete information about what avenues have been pursued by other researchers, particularly those in industry. Even where needs are clear, there are limits to the ability of current research funding mechanisms to encourage progress on the most fundamental questions.

Pew has convened experts to identify barriers to scientific breakthroughs in antibiotic drug discovery and develop a roadmap for addressing them. That process is ongoing, but initial discussions have identified factors such as inter-disciplinary expertise, co-location, common mission/goals, and sustained funding efforts as crucial for making headway. These are features that may be difficult to capture with traditional "bottom-up" funding mechanisms.

CONCLUSION

The medical products ecosystem continues to produce innovative products that, in aggregate, benefit Americans and improve health. Products with the greatest potential to address unmet medical needs enjoy a variety of advantages that speed development and review. The FDA, lawmakers, industry, clinicians, patients, venture capitalists, and other interested stakeholders share complementary goals: ensuring that patients have access to safe and effective novel medical products and enabling U.S. companies to stay competitive.

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The CHAIRMAN. Thank you very much. Thanks for the excellent testimony. We'll now begin a round of 5-minute questions.

Dr. Sullenger, the National Academies has done two studies that show that 42 percent of the investigators' time on research grants is spent on administrative matters. I asked the head of the National Academies what he thought might be a reasonable amount of time. He said it would vary depending on the grant, but maybe 10 percent.

Congress appropriated $30 billion to the NIH, 80 percent of which goes to extramural research mostly at universities. Vanderbilt University did a study in conjunction with a report that Senators Mikulski, Bennet, Burr and I asked for about Federal regulation of higher education.

Vanderbilt, based on their figures, would roughly say that a quarter of all the research dollars that they get goes to administrative costs. That would be about $125 million out of $500 million, more or less.

What's your reaction to that? What do you see at Duke, and what suggestions do you have for reducing that problem? If we could save billions of dollars there, that would be one place to get more money for new investigations.

Mr. SULLENGER. Thank you for the question, Senator Alexander. I would say my general impression is it's a similar number. We're spending increasing amounts of time on regulatory issues. Some of them don't seem to even pass the commonsense test, I would say, in some sense.

For example, in my group, we study blood coagulation. We draw blood from healthy volunteers. But regulatory requirements for doing that, which doesn't really put anybody at much risk, is similar to you doing a clinical trial with a new drug. So at some level, stratifying and applying some commonsense measures to the regulatory issue would help a lot.

The other challenge with administrative burden goes back to what the whole group or, at least, the panelists have mentioned, which is the stress that we have on the NIH funding system. It means that each investigator is writing many more grants, going through all the process of administering, doing the budgets for the grants, et cetera, which takes a tremendous amount of time.

The math is pretty simple. It's basically that now it's about half—we have about half the probability of getting a grant as we

did a decade ago. That means to get two or three grants, we're writing four or eight times as many grants over a 4-year period to get the same amount of support for research.

The CHAIRMAN. I understand that. But what is your reaction to the suggestion that the 42 percent figure, in terms of the amount of time spent, might be closer to 10 percent? Does that sound reasonable to you?

Mr. SULLENGER. Ten percent may be tough. I think to get there, what we have to think about—and one of the things we've tried to do in our institute is to basically borrow from the private sector some of the strategists they use, to say,

> "Could we get sort of professional project leaders who are much less expensive and much better trained to do these things to reduce that burden."

The CHAIRMAN. But if we only got it from 42 percent to 20 percent or 25 percent, we're talking billions of dollars of Federal taxpayer dollars that could be used for research, not necessarily as a substitute for increased funding, but as one way to find more dollars.

Mr. SULLENGER. I absolutely agree with that. I think that reducing those burdens is a way to find a big cost savings, and also let researchers spend their time on what they're trained to really do, which is to do the science.

The CHAIRMAN. I want to stay within my time. Let me ask Mr. Borisy this question, and others of you may want to talk about it. Dr. Hamburg said at our hearing that the FDA had a record number of new drug approvals last year and talked about the breakthrough therapies program.

She said,

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

Any comment on that?

Mr. BORISY. I think those numbers are accurate. If you are developing a drug in an area that will qualify for accelerated approval or the breakthrough therapy designation, I think that's a very productive interaction with the agency. If you are out of those areas, then there becomes a lot more uncertainty and a lot higher degree of questions.

The CHAIRMAN. Mr. Mussallem.

Mr. MUSSALLEM. Yes, I think those numbers are accurate. I'm not sure that that experience necessarily translates over to the medical technology and diagnostics side. By and large, although those trends are positive and there are some great moves on the part of leadership in the right direction, there has not been that sort of trajectory that's going on in devices.

The CHAIRMAN. Thank you. My 5 minutes is up.

Senator Murray.

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

Mr. Mussallem, let me start with you. Your company has made some really significant advances in medical device product development. Your testimony talked about both the regulatory challenges you face as well as the progress that is being made at the FDA.

Can you tell us more about how you have seen FDA engaging with developers and the effect that it's having on the development of new therapies?

Mr. MUSSALLEM. Yes. I'm very encouraged by what's going on with the leadership of FDA, particularly on the device side. Dr. Shuren and company have reached out to the industry and really tried to advance an agenda that is responsive to the feedback that they've gotten. Frankly, they've been disappointed with what's happened in the past, and trends are going in the right direction.

I do think also that they're managing quite a large bureaucracy, and it's not so easy to move sort of the day in and day out bureaucracy at the same pace that leadership is moving, which is why we encourage that to continue. There's a particular initiative called MDIC, which is a public and private partnership, which really gets deeper into regulatory science which could be a really good example of the way to make advancements.

Senator MURRAY. Thank you.

Mr. Coukell, in your written testimony, you discussed innovative ways to perform clinical trials so that trials are more flexible and efficient. You stressed that the data collected through robust clinical trials is critical and provides patients and healthcare providers the information they need so they can make well-informed decisions.

Can you discuss in more detail how we can move forward with innovative clinical trials without compromising the data needed to help patients and healthcare providers make informed decisions about their products?

Mr. COUKELL. Thank you for that question. I think that the key point is that the randomized trial has been an essential tool in figuring out if something works, and we have a legacy of examples where we didn't do a randomized trial and only later learned that it was not working or causing harm.

But it has become increasingly expensive to do these trials. I talked in my testimony about ways that we could get better at pulling information out of the electronic health record to do trials. We also need to get faster at the contracting process, at the consent process, at the institutional review board process. All of these things could help streamline trials.

We could use more clinical trial networks to get better at finding patients. The Scandinavian trial that I mentioned in my statement enrolled half of all patients getting that particular procedure. If we could populate our trials faster, just take advantage of the patients that are already in our healthcare system now, the time it would take to do a trial—and time is money—would be so much shorter.

Senator MURRAY. I've heard from a lot of families in my home State of Washington about the terrible situation of a loved one having a disease and there's no treatment available. I know we all have, which is part of the reason why we in Congress put in place the FDA breakthrough designation and accelerated drug approval in 2012.

Can you talk a little bit about how these new authorities are working to help meet the serious medical needs of patients?

Mr. COUKELL. The breakthrough therapy is widely viewed to have been a success. It's essentially an all hands on deck approach, where if a new drug is identified as being especially promising or an especially important advance, the agency puts everything in service to get that review done faster. It doesn't change the upstream evidentiary standard. But it does help get those products to market more quickly.

Senator MURRAY. One last question for you. We're all about helping patients. That's basically the backbone of everything we do. As I mentioned earlier, the perspective of patients and their families has to be prioritized in the product development and approval process.

I know you've spent a lot of time examining that issue. Can you tell us more about how you believe patients can be more involved in this process?

Mr. COUKELL. Senator, I think you're absolutely right. At the end of the day, what matters is the patient experience, and that's suitable for some indications and not others. It doesn't matter too much for a blood pressure drug. But if you were treating something like arthritis, understanding how it has actually influenced the patient's life, their function, their quality of life is really fundamentally the most important thing.

Those patient-reported outcomes are still challenging to measure and challenging to know how much of a change matters. So measurement remains hard. But building those kinds of things into our assessment of new medical technologies is really important.

Senator MURRAY. Thank you. I really appreciate that.

My time is up, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray.

Senator Cassidy and then Senator Mikulski.

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. Implicit in what you were saying is that different divisions of the FDA have different rates of approval.

I have something from the Manhattan Institute which shows that oncology and antiviral has a median time and a mean time of approval substantially better than that for neurology, cardiovascular, and renal.

I'm trying to understand why some divisions at FDA do really well, and others, at least judged by time to approval, do far less well. Do you have thoughts on that? Because implicit in your testimony is that people acknowledge that there's differences—I think you mentioned several times diabetes and Alzheimer's as being something—I think it was your testimony—as having delayed approval times.

Any thoughts on that? Can we understand why some divisions do well and others do poorly?

Mr. COUKELL. I think it's a crucial question, and I'm not sure I have a good answer. Part of it is leadership and engagement with the stakeholder community. I think that one of the things that we have seen happening, in particular, over the past 6 years is this

increasing focus on public-private partnerships to develop the kinds of regulatory tools that we need to assess——

Senator CASSIDY. I see that oncology has like 200 days, whereas neurology has close to 600, as a median time to approval by FDA division. Again, your survey seemed to find that different groups found that, oh, yes, the FDA is working well, and other groups found that FDA is not working very well.

So if you did a crosstab, would the people that found FDA working well—would those be the oncologic researchers? And those that found it working less well—would those be the diabetes researchers?

Sir, you're shaking your head. You're nodding as if you agree. Can you comment on this?

Mr. BORISY. Yes. I think you would tend to find those differences by the different groupings within the agency. Some of those are people related, cultural related. It is a very large agency, as was mentioned.

Senator CASSIDY. I keep hearing people and leadership. Dr. Hamburg, for example, has done a great job. We can see all these improvements. So it tells me that it's division leadership. It's not necessarily overall leadership. I'm not putting you on the spot, because I don't want to sabotage any approvals that you have currently before a division.

[Laughter.]

But I am struck that there must be some sublevel division that is not working as well, that is keeping needed drugs for diabetes, et cetera, from being approved in a more rapid fashion.

Mr. BORISY. I would agree with your statement that there's been strong senior level leadership, and we need to pay attention to making sure that we continue to have consistent senior leadership at the agency going forward. A question is how can we help the agency from a human resources perspective, from a—hiring the talent that's necessary throughout the agency, to be able to take the——

Senator CASSIDY. First, let me say somebody's testimony spoke—and maybe Pew's—as to how we should have people surveyed, so there should be more training. In another document, in another hearing, I think I read that the average person studies for 2 years before they become a reviewer. I'm thinking, "Oh, my gosh. If we have more training than 2 more years, this is a master's." The University of Maryland now has master's training for becoming an FDA reviewer.

At some point, there has to be something besides training which is a solution. I guess I'm trying to put my finger on what that training is.

Mike.

Mr. MUSSALLEM. In a slightly related subject, there's a vast difference between devices and diagnostics inside the FDA, and it goes on in drugs and biologics. That's just because there's a different development process, and it deserves a different regulatory system. Devices are developed with engineers and scientists working closely with doctors, and then there's an iterative process in which there's a rapid improvement that takes place rather than a single entity——

Senator CASSIDY. Can I interrupt you because I'm almost out of time.

Mr. MUSSALLEM. Yes.

Senator CASSIDY. I've also noted, again in someone's testimony—they're jumbled together—that in some cases, there is a sort of collaborative iterative process. In the other, they look for guidance, and it's the guidance which is not quite as useful.

Are there some divisions that are better at giving this constant communication, and are there others that put out guidance that is like reading tea leaves and you're not quite sure? Is that part of what this leadership is about? We need to understand why FDA works really well for onc and poorly for Alzheimer's drugs. Do you follow what I'm saying? Are there some divisions that are better, given this iterative interactive process and others not?

Mr. BORISY. There are some divisions where the accelerated approval pathway is more directly applicable to. In other words, just the diseases and the conditions those divisions are treating have been under accelerated approval. Then with breakthrough therapy that is having the clear sense of Congress, as was legislated in FDASIA, that made a big difference throughout the agency, not only at the senior leadership level, but throughout the depth of the agency.

The communication of policy from Congress does have a big effect on the agency. Different groups have had more experience with the accelerated approval because the way that's written, it applies more to some disease areas than to others.

Senator CASSIDY. I yield back. Thank you.

The CHAIRMAN. Thank you, Senator Cassidy.

Senator Mikulski.

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Thank you, Mr. Chairman. I really want to thank this panel for a very content-rich testimony.

My interest in this is threefold. No. 1 is to improve the lives, save the lives of people both in our own country and around the world, to have clinical products that actually improve their lives. I'm also interested in the jobs that are created by having them right here in the United States of America.

Mr. Borisy, your description of your life and your companies are very similar to Maryland. We have FDA, we have NIH, and great institutions at Maryland, and Hopkins, and then, of course, our vibrant biotech industry. But the other is also to be able to export products, because if they do have the FDA approval, we can sell easily abroad, particularly to countries that don't have the FDA. So that's where I come in.

Let me go to my questions. Much has been said about FDA and its approval process. My question is this. In the approval process at FDA, do you feel that not only does it require leadership, but certainty of leadership, and then certainty of financial resources? In other words, that FDA really knows what it's going to get, and it can really count on it, that NIH and its institute directors, not only the CEO of NIH, the director, but the institutes.

Do you feel that reliability, certainty, and predictability of what they will get from the government budget is essential to both the

recruitment, hiring, and kind of the experience needed in the regulatory process?

Mr. Borisy, you and then Mr. Mussallem.

Mr. BORISY. Yes. Stability at the agency, both in terms of leadership and resources so that we can have a stable and predictable regulatory process is very important.

Senator MIKULSKI. Why do you say that?

Mr. BORISY. In creating innovation, in funding new companies, which we do at Third Rock, we're embarking on a journey that's a 10- to 15-year product development cycle that will cost—the total journey—north of a billion dollars. That is a long time and a lot of money.

When we start that in the beginning, we're trying to say: What is the path of that going forward? How much will be spent when? When will we get to what point? When will we be able to show things to convince other people downstream that value has been created?

So much of that interaction is with the agency. Knowing what those paths will be, knowing how much it will take, and what the hurdles will be is crucial. If those change unexpectedly, it makes it impossible to be able to invest that type of resources over those types of timelines.

Senator MIKULSKI. Mr. Mussallem.

Mr. MUSSALLEM. Yes. In terms of creating jobs and making a commitment from the private sector, certainty is very helpful, and so we ask for a certainty in our regulatory processes. If you just move upstream from that, the point that you're making, Senator, about them having certainty in their funding is certainly aligned with that.

If they have the ability to count on the resources, and they can make the investments in training to keep up with the rapid advancements and technology that they're going to be constantly dealing with in the future, it puts them in a far better position to be able to deliver what we need from them, which is an efficient process that really, in a timely fashion, moves through these processes.

Senator MIKULSKI. First of all, respect to the people who work there, because their morale is absolutely important. There's a whole culture in Washington—let's blame the bureaucrat, let's not fund them, and then let's complain when the job doesn't get done—so starting with respect. But resources can't be like a one-shot deal. It has to have continuity and stability.

No. 3 is targeted reform. I'm very much interested in the fact—what you said, Mr. Coukell, which is that one set of processes costs hundreds of millions of dollars. Using new techniques could reduce it to like $300,000. That's a stunning number.

Are you saying that registries would be the answer to all problems? Or what would be the limitations of registries?

Mr. COUKELL. I wish there was a single answer to the problems.

Senator MIKULSKI. So do I.

Mr. COUKELL. Unfortunately, there isn't. I think that being able to get better at extracting the information from our healthcare system, finding patients, putting them into trials, learning before and after a product reaches market from the information that's in the

electronic health record, and being able to do it in a more cost effective way would be a very important contribution. It, unfortunately, won't solve all problems, and we have to take a broad-based look at other approaches to reducing the cost of acquiring clinical data.

Senator MIKULSKI. My time is up. Mr. Chairman and colleagues, we have a big opportunity, that in this budget debate we could end sequester, which is very demoralizing and disruptive. We want disruptive technologies, but not disruption in resources.

We could also lift the caps. I know there's a big move to lift the caps in defense, and, of course, we worry about the threats to America. But there are these other threats that these men and women have devoted their lives to fighting, the threats of arthritis, depression, and Alzheimer's and all these things, and cystic fibrosis.

I think we ought to just lift the caps and end sequester, it would be a big down payment on what is being recommended here.

The CHAIRMAN. Thank you, Senator Mikulski.

Senator Burr.

Senator BURR. Thank you, Mr. Chairman.

Mr. Coukell, should the FDA be required to use foreign clinical data as they review and approve new applications?

Mr. COUKELL. The short answer, sir, is no. If a trial was conducted outside the United States, and it was a patient population that wasn't like ours, or we had reason to believe the trial was badly conducted, we wouldn't want that to go into our evaluation of a product.

But should they be able to, and do they use clinical data that's generated outside the United States? Absolutely.

Senator BURR. They've had that ability since 1997 and rarely chose to do it. And in cases where applicants have asked the FDA to use foreign clinical data, because the population was similar or there was merit to it, the FDA's response has been we weren't involved in the consultation of how the trial was designed. Therefore, we can't use the data. Do you call that cooperative and helpful?

Mr. COUKELL. Sir, I served for a couple of years on the Cardiovascular and Renal Drugs Advisory Committee, and I would say virtually every product we looked at brought data from both the United States and outside the United States.

Senator BURR. Mike, the FDA Act of 1997 required the FDA to eliminate unnecessary burdens that may delay the marketing of beneficial new products. But the statutory requirements for clearance and approval remained exactly the same. The goal of least burdensome requirements was to streamline the regulatory process and reduce burdens to improve patient access to breakthrough therapies.

In your opinion, is the letter and the spirit of the least burdensome provision being applied on a day-to-day basis at the agency?

Mr. MUSSALLEM. Thank you, Senator. You're onto a very key point. It's been there. It's been in the background. But my sense is that least burdensome needs to be revitalized. It needs to be focused on.

I think of all the new reviewers that have come into FDA as part of the recent funding from industry. I wonder how much training

they've really had on least burdensome and how to really bring that to practice. There's something there that's valuable, and it's one that we should encourage FDA to look at even more seriously than they do today.

Senator BURR. Thank you.

Dr. Sullenger, earlier this year, the Chairman and I penned our Innovation for Healthier Americans report in which we asked the simple but critical question: How can we do medical product research and development better on behalf of America's patients?

Based on your experiences across the pipeline, are there specific proposals or ideas that you would encourage us to focus on in this committee as we examine that critical question?

Mr. SULLENGER. One of the things that we're very interested in is how do we educate people to be thinking along those lines more. Traditionally, I would say most of our science training isn't focused in this translational space that you're alluding to, which is how do we take innovation and apply it to help improve healthcare.

I was fortunate enough that—there have been some pilot programs along this way. The Howard Hughes Medical Institute actually had a pilot program of trying to train scientists to work more at the medical interface. They hoped that the NIH would pick up that program after they seeded it, and because of the budget issues, they haven't.

One of the practical things I would recommend is considering sort of training this next workforce to do exactly what you're saying, to teach scientists to think at that interface versus doing pure fundamental basic science. We need both. Just like we need chemists and chemical engineers, we need molecular scientists and we need applied molecular scientists.

Senator BURR. We're in a new area, aren't we?

Mr. SULLENGER. Absolutely.

Senator BURR. Mr. Borisy, in your testimony, you note that medical device and diagnostic venture capital investment was down 27 percent from its peak in 2008 of $3.6 billion, and that in 2014, first-time investments in medical device companies fell to the lowest number of companies since 1995. What do you believe to be the largest contributing factor to that decline?

Mr. BORISY. It's a very real decline. Actually, in our own funds, we've made several device investments in our first fund, and we're now down to one single investment that we're making out of our current fund. It's a double jeopardy of an unclear regulatory hurdle, which has been lengthening, coupled with an unclear reimbursement hurdle.

In both medical devices and diagnostics, after the product is approved, it conventionally takes 2 to 5 years of hashing out and debate both with Medicare and private payers to secure reimbursement. If you increase the regulatory requirements, which is what has happened over the past decade in devices, but you have unclarity in how it's going to get paid for, then the math just doesn't work, and then the investments can't flow.

Senator BURR. Mr. Chairman, if I could just ask one more question, and it's a hypothetical question for Dr. Sullenger.

Should the FDA be able to regulate anything that I take from my body, don't alter, and reintroduce into my body?

Mr. SULLENGER. That's a good question. I don't know that—I haven't thought exactly about that. But one of the programs we look at is bone marrow and cord blood transplant for patients. And, essentially, it's doing those types of procedures.

We take cord blood at Duke from babies and then re-implant it to them after they're born, and there is a regulatory requirement for that. It's less than if we've manipulated or changed those cells, but there's definitely some regulatory requirements. I could seek advice from the people doing that at Duke, but I'm not an expert in it.

Senator BURR. I'd just pose to all of you as we talk about this different path forward, this different world, that we're going to be faced with decisions that don't look like the decisions today. They're not black and they're not white. I could make a tremendous case today that why should the FDA regulate what I take from my body and put back in my body, and I think that the body is the greatest source of cures in the future. It's just understanding what it is you use and where you use it.

I thank the Chairman.

The CHAIRMAN. Thank you, Senator Burr.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman.

Mr. Borisy, just picking up a little bit on Senator Burr's previous question, a number of years ago, he and I and Senator Hatch, I think, all heard that venture capital—or from our bioscience communities that venture capital was no longer investing in the United States in this area. It was going to Europe and it was going to Asia. And they came and said, "Is there something you can do to help us with that?" And that became breakthrough therapies.

I think your testimony today, and the rest of the witnesses' testimony, is that it's actually been a pretty big success. I wonder if you could talk about, in very practical terms, how that has helped your ability to invest here in the United States.

And, Mr. Mussallem, I'll come to you to talk about your ideas for the breakthrough therapy technology designation and what that might look like.

Mr. Borisy, I'll start with you. You described it as productive interaction with the agency—is what you said around breakthrough.

Mr. BORISY. In creating a new medical product and a new drug, it's this long path and more than a billion dollars to create it. As a venture capital firm—and we are one of the larger venture capital firms, and we put more money into a typical investment than most—we might invest $30 million or $40 million or $50 million into a company. That's only a small piece along that billion dollar journey.

Getting to a point of clinical proof of concept, where you clearly know that you've done something important for a patient, that often is going to cost on the order of $200 million to $250 million. So when we create a company and invest in a company, we're looking to understand the path of what partners might join us on that,

whether those are larger companies or whether those are public markets.

Part of what they want to know is: Will we have clarity that you really have done something that's important? Because one of the great things of the overall ecosystem here in America is that if you have shown something in patients, that it really is doing something that people believe is important, they'll value that very highly, and that makes this whole set of equations in this ecosystem work.

Having breakthrough therapy, having accelerated approval, having those tools so that in the areas where they apply, you know that with those initial clinical studies and the results you get, if the science and medicine is good, if the results are worthy of it, then everybody in the ecosystem values what has been created.

That makes it possible that those really early stage investments, when we're investing for things just coming out of academia and doing that initial work, can be done, because we don't have to go all the way—the 10 to 15 years to approval. We can fund it for the 5 years, 6 years to that clinical proof of concept, and so the equation is solved. On medical devices, those equations aren't solving right now, because everything is too unclear.

Senator BENNET. Mr. Mussallem.

Mr. MUSSALLEM. Yes. Mr. Borisy makes great points. Thanks, Senator. You're onto an important theme. We can take some of the lessons that have been learned on the drug side for breakthrough therapies and apply it to the medical technology and device side.

Today, we don't have that sort of pathway. I would suggest that an expedited pathway for truly important medical technologies that are really transformative and breakthrough should be adopted, and that could make a difference.

You could get bogged down if you try to move every medical device through that sort of a system. But for the ones that are most important, there's a big positive that's associated with that that can make for the kind of policy success that we've seen on the drug side.

Senator BENNET. Somebody testified—it may have been you, Mr. Borisy—that the breakthrough sort of—that the message from Congress had been heard by the FDA, not just at the top, but all the way through the agency. Can you talk a little bit more about that, too, as we think about cultural change?

Mr. BORISY. That's a very important point, because when FDASIA was being passed that authorized the breakthrough therapy designation, a lot of the arguments or discussion going on at the time said: Why does this need to happen? The agency already has these authorities.

Yet we can see that having had that in an act of Congress, in FDASIA, establishing the breakthrough therapy really has had a dramatic effect. That goes directly into what I do in new company creation.

When we think about different areas, when we're just talking about a breakthrough therapy for medical devices, I know a lot of thought has been going into anti-bacterial—to bacterial resistance and also can go into other areas, as has been mentioned, diabetes, obesity, depression, Alzheimer's, places where you can say can we

create clearly understood patient populations, precision medicine, the right drug for the right patient.

If we can get clear pathways so it's limited populations, where one can understand and deploy the successful lessons of breakthrough therapy, then that act of Congress really had a tremendous effect across the agency.

Senator BENNET. Thank you to the panel. I'm out of time.

Mr. Chairman, thank you very much for holding this hearing. I hope in the coming weeks, as we work together to figure out what the next generation is, that we'll have the chance to work together on it. It's very exciting.

Thank you.

The CHAIRMAN. Thank you, Senator Bennet.

Senator Franken.

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman.

Mr. Mussallem, you mentioned in your testimony here the Medical Device Innovation Consortium, which kind of started with the LifeScience Alley in Minnesota, working with the FDA. When Commissioner Hamburg was here, I asked her how public-private partnerships like the MDIC help to improve relations between regulators and the industry. In your written testimony, you mentioned that Edwards Lifesciences has seen positive improvement in its dealings with the FDA.

How can we expand the MDIC model to continue to foster the strong positive relationships between industry and regulators? And can you describe how it has improved thus far?

Mr. MUSSALLEM. Thank you, Senator. You're onto something. I may not be an expert here in the statutory limitations in terms of conversations between regulators and companies, but through this public-private partnership, we have a chance to have intimate conversations about regulatory science and how to do it better and how to have an open and honest dialog about what's working and what could be better. I think that the agency and the industry finds this kind of dialog really refreshing, and there's learning that comes from that.

One of the things most tangible for me is we're working now on a tool to be able to incorporate the patient's voice somehow into the regulatory process, because that's been missing in the past. That's one that comes to life very specifically when you work on these breakthrough technologies, in particular.

Senator FRANKEN. When I first came to the Senate and started studying these kinds of issues, I saw the different culture between the regulators, of course, and the industry, and this public-private partnership—and this is the first of its kind—seems to be very helpful.

Mr. Coukell, in your testimony, you discuss several ways to improve clinical trial efficiency, and one of them is by streamlining the institutional review board, the IRB process. My understanding is that under current law, if a medical device company is testing a device in multiple locations, they need to get IRB approval in each location where they're conducting the trial.

You suggested that this process could be centralized in a single national IRB in order to improve efficiencies. Could you elaborate on that?

Mr. COUKELL. Yes, sir. One of many steps that takes time when building a clinical trial is going to the institutional review board to review the trial from a perspective of patient safety. As you say, for medical devices, now the law requires that that be done locally. There are examples in other therapeutic areas of using a single centralized board, and that is one thing that could speed up the process of standing up a new trial, if that prohibition on centralizing was removed.

Senator FRANKEN. Thank you. You also talked about the role that disease and device registries can play in making data collection more efficient. Mr. Mussallem testified that his company used a registry, a large data base of patient information, as a key part of getting one of his products approved for a new use. You talked about a trial in Sweden where researchers were able to leverage an existing cardiovascular disease registry to study a lot of patients for a fraction of what it would cost in the United States.

What are the barriers to expanding the use of registries in the medical device approval process?

Mr. COUKELL. There are several. One is getting the data into the database. Right now, for a lot of these registries, it requires somebody to hand enter it. In some cases, it's taking more time to enter the data in the registry than it is to actually carry out the procedure. So if we were better at pulling that from the electronic health record, or at least some of the data from the electronic health record, it would reduce the cost of operating the registry.

We also have to recognize that right now, we're building them one at a time, and we're doing it in a costly way. We need a sustainable funding model that will let us operate them at a lower cost.

Senator FRANKEN. Thank you. I was going to ask Mr. Mussallem about his opinion on registries, but——

Mr. MUSSALLEM. Just quickly, it's a very powerful tool. It can really work. Allan said it well. We need not to overreach for this—try and find really the data elements you really need, and if you can automatically populate it so you don't make this another big administrative burden for hospitals.

Our case was a perfect one. It actually takes twice or three times as long to fill out the registry as it does to do the case, and that's not helpful. But there are best examples that can be applied, and this can really be powerful, because by being able to collect vast amounts of information on all the patients that are being treated, you can make some very informed decisions on efficacy and safety, for that matter.

Senator FRANKEN. Thank you.

Thank you, Mr. Chairman. We probably should do a hearing sometime on electronic medical records. Oh, we just did. I'm sorry.

The CHAIRMAN. We'll do some more. Actually, we're going to focus more on electronic medical records. Based on that hearing we had, there's a lot of interest on both sides, and I talked with the acting director of CMS, who is interested in taking some steps.

That's probably an area that we might work on and see if we can get a result.

Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman.

Every single Member of Congress I've spoken with says that they support NIH and they support more medical research. But medical research takes money, and Congress has done absolutely nothing to actually get more money into the agency. In fact, for over 10 years, Congress has been choking off vital funding for medical research and has reduced the buying power of the National Institutes of Health by nearly 25 percent.

All of you work in different parts of the American system of medical innovation. Can you tell me in just a few words how gutting NIH funding over the last decade has affected your sector?

Mr. Borisy, could I start with you?

Mr. BORISY. Yes. Our historical investment in NIH has been absolutely the basis of our life sciences ecosystem and all the innovation that we have here in this country and is absolutely essential for the future.

The diminishing of resources that we're facing now—I see it in two ways that it's affecting. One is going to be long term. There's obviously great breakthroughs in science and medicine that have been happening from the investments that we've made over the past decades. Those are still good right now.

But those aren't going to be there in 10 or 20 years. It's a long-term cost to one of the most dynamic sectors of our economy and also that does so many things for patients.

A second thing, which I will admit in the short term is beneficial, but is not good for the ecosystem in the long term—when I'm looking to hire people now, I'm able to hire people that would have been getting—would have been the new stars, the rising stars, the people that would be getting the junior faculty positions. I'm also able to hire people out of the more senior faculty positions. The best talent that used to be going into academia, I am now able to hire into the companies that we're creating.

This is good in the short term for the companies. It's not good in the long term, because these people, in the past, would have gone on to amazing academic efforts, which would have spawned many, many companies, many, many innovations. So you're seeing that it's a direct effect.

Senator WARREN. Thank you. This is very powerful, but I'm also going to have to ask you to be short if you can.

Mr. Sullenger, could you just add something from your field?

Mr. SULLENGER. Yes. From being on the academic side, it's been crippling, to be blunt. I would echo several of the things that my colleagues are saying. Not only are we losing people from the academic sector to the private sector, but we're losing them to other countries. Now we're having a loss of our best and brightest, who are leaving the United States to go to Asia because they're investing more. It's been crippling, to be sure.

Senator WARREN. Thank you.

Mr. Mussallem, could you add something?

Mr. MUSSALLEM. Yes. I believe NIH funding is a critical element, and it really has a great return on investment. That early investment in research answers some key questions that then causes the private sector, like us, to jump in and move products to patients, so there's a return on investment. When you get that early research right and you answer some tough questions, then you encourage others to follow.

Senator WARREN. A critical part of the pipeline.

Mr. Coukell.

Mr. COUKELL. In antibiotic development, which is a particular focus for us, we have a 30-year drought of new drugs, and we have some basic upstream science questions that really need to be answered if we're going to jumpstart the pipeline. There are questions that companies aren't in a position anymore to address.

Senator WARREN. I want to thank all of you. The House Republican budget and the Senate Republican budget were both released last week, and both say that they support medical research funding. But what the Republican budgets actually do is lower the budget caps that are already crushing our research agencies, making it likely that agencies like NIH would see cuts, not increases, under these plans.

Chairman Upton, who is leading the push in the House for FDA reform, says he cares about research, too, and says that the NIH needs more funding. But his draft bill, called 21st Century Cures, doesn't provide a single new dollar from Congress for NIH, not one dollar. Talk is cheap.

Earlier this year, I introduced a proposal to try to fix this problem. The Medical Innovation Act would boost the NIH budget by about 20 percent, and it achieves that increase without raising taxes, without gutting vital programs, and without adding to the deficit. More than 30 nonpolitical doctor, patient, and scientific organizations, like the American College of Surgeons, the National Women's Health Network, and the Dana-Farber Cancer Institute, have supported it.

There's no reason that every Republican, Democrat, and Independent in Congress shouldn't be able to support it. If people don't like this idea, then they should bring other solutions to the table. But let's be clear. It doesn't matter what Republicans say about supporting innovation if their budgets actually cut support for NIH. It doesn't matter that House Republicans put the word, cure, in the name of a bill if the bill doesn't put one new dollar from Congress into NIH to help fund those cures.

Something needs to change. Families are losing loved ones to incurable and untreatable diseases while we do nothing. It is time for Congress to stop talking about increasing medical research funding and actually do something about it. People are counting on us.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Warren.

I want to thank the witnesses. Several Senators said as they left how—as Senator Mikulski said—content-rich the testimony has been. I want to thank Senator Murray for working together with me to do this.

I'll ask Senator Murray if she has any further comments to make, and then we'll conclude the hearing.

Senator MURRAY. Thank you very much, Mr. Chairman, and I am very worried about sequestration and budget cuts and the impact on our ability to make sure our families have the cures that they are really counting on. We've seen a lot of advances in medical innovation that have improved the health of families and helped our economy. So it really is critical that we meet these challenges that have been outlined today by this excellent panel, and I really appreciate your input.

Mr. Chairman, I look forward to working with you on finding bipartisan ways to continue the success we've had in the past to advance medical innovation.

The CHAIRMAN. Thank you, Senator Murray.

These things occur to me listening to what was said today. Reimbursement is something we need to focus on. The acting head of CMS mentioned, I believe, that the cost of reimbursing for hepatitis C grew from a few hundred million last year to $6 billion, a great success, a cure. But that's a lot of money.

Another company told me that while they're losing hundreds of millions of dollars a year, they're producing a new breakthrough therapy that will cure a dreaded disease. Its annual cost is going to be a few hundred thousand dollars. These are things we want to do. But we have a lot of tough choices coming up as we think about reimbursement in the future.

It was important to hear that attention from Congress matters. The point that the FDA—the breakthrough authorities that it needed were already in the law, but the fact that the new law came in seemed to put an emphasis on it. That's useful to us.

It's important, too, in terms of the funding, on the point of increasing funding for NIH, there is widespread—well, I'll just speak for myself. I think we should do that.

It would be poor management not to pay attention to the National Academies saying that of the $24 billion we spend in extramural research, mostly at research universities every year, 42 percent of it goes for administrative costs. If we can get that down to 32 percent, that's $2 billion or $3 billion more. That's real money that we're already appropriating, and I hope we can work together to also do that while we're talking about increasing the total amount.

Then it's inescapable that if we're looking at our budget, the side of the budget that has to do with military spending, cancer research, NIH, is about level funding over the next 10 years, more or less. The side that has to do with mandatory entitlement spending goes up 86 percent over the next 10 years. Yet Democrats and Republicans are wary of doing anything about this.

I've said many times the fact is unless we do something about this, we'll never be able to do anything about this. It's going to squeeze out the money that would go for all the things we're talking about today. That's a spirited discussion that we can continue to have.

But I would ask, finally, that each of you, after you leave, if you reflect on anything that you'd like to say to us in terms of specific steps you'd like for the Congress to take, I hope you would do that.

I have a little ritual I have to go through at the end here, and it's written on this piece of paper.

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

The next hearing on medical innovation is tentatively scheduled for April 28th.

Thank you for being here. The committee will stand adjourned.

[Additional Material follows.]

ADDITIONAL MATERIAL

DUKE UNIVERSITY MEDICAL CENTER,
APRIL 28, 2015.

Hon. LAMAR ALEXANDER, *Chairman*,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

DEAR CHAIRMAN ALEXANDER: As director of the Duke Translational Research Institute and professor of surgery at Duke University Medical Center, I am pleased to submit additional feedback following the March 24, 2015 hearing entitled, "Continuing America's Leadership: Advancing Research and Development for Patients." I appreciated the opportunity to participate, and we are grateful for your leadership in exploring thoughtful and meaningful reform of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).

I have attached additional information in support of my written and verbal testimony in response to the additional queries made by various committee members. We look forward to continuing to work with the committee as it continues examining the time and cost currently involved with the drug and medical device discovery and development process, and how to better align public policies to support medical innovation.

If you have any questions or need additional information, please feel free to contact me at *Bruce.Sullenger@duke.edu* or (919) 684-6375 or Catherine Liao in the Duke Medicine Office of Government Relations at (919) 416-8913 or *Catherine.Liao@duke.edu*.

Sincerely,

BRUCE SULLENGER, PH.D.,
Joseph and Dorothy Beard Professor,
Director, Duke Translational Research Institute,
Department of Surgery,
Duke University Medical Center.

RESPONSE TO QUESTIONS OF SENATOR ALEXANDER, SENATOR ISAKSON, SENATOR COLLINS, AND SENATOR WHITEHOUSE BY BRUCE SULLENGER, PH.D.

Since many of the queries involve challenges between the academic and private sectors and difficulties with translating medical innovations from the laboratory to the community, I have discussed these questions with Dr. David Robinson, Professor of Finance in Duke's Fuqua School of Business and Research Director for the Duke Center for Entrepreneurship and Innovation (*https://www.fuqua.duke.edu/faculty_research/faculty_directory/robinson/*). The responses below incorporate some of Dr. Robinson's thoughts and recommendations.

SENATOR ALEXANDER

Question 1. What barriers are there to academic medical centers collaborating with other private entities, such as drug and device companies?

Answer 1. We believe that the main impediments preventing academic centers from collaborating more effectively with private entities are the rules in place inside the university, especially as they pertain to conflict of interest and licensing policies. As I mentioned in my introductory remarks, currently the NIH requires academic institutions to disclose and mitigate conflicts of interest between faculty and private entities. Because the safest way to mitigate such conflicts is to limit such interactions, often policies are established at risk adverse, academic institutions that serve as barriers that faculty must overcome if they want to interact with the private sector. Thus I would recommend that the NIH work with Congress to clarify and simply what is allowed or even encouraged with regard to such interactions.

University licensing policies can also be a barrier for such collaborations. To the extent that University Offices of Licensing and Ventures favor early licensing revenues over long-term business value creation, they inhibit the creation of new businesses formed around technologies. To the extent that strategic alliance funding is an important source of capital for such firms, this in turn inhibits collaboration between academic medical centers and other private entities.

Question 2. We do not want to waste time this year, and want to focus on the areas that have the greatest impact on improving our biomedical research enter-

prise. What are the two or three things that, if done right, would help you accomplish your goals?

Answer 2. In addition to addressing the challenge associated with conflict of interest described above, I would reiterate three tractable issues I mentioned in my statement as well as add a fourth that I believe the HELP Senate Committee should focus upon with the NIH, FDA, academic community and private sector:

1. To train and expand a biomedical research workforce that is ready to utilize and act upon the genomic and informatics revolution;
2. To rebalance and right-size support for all phases of biomedical research as we transition from gathering intelligence on health and disease (basic research) to rationally using the large amounts of information to combat disease (translational and clinical research);
3. To reduce the administrative and compliance burdens placed upon investigators and academic institutions to reduce costs and improve productivity; and
4. To reduce regulatory uncertainty to release the brakes on private sector investment in biomedical research. Whether FDA regulatory waiting times are long or short is secondary in some sense to whether they are predictable. Anything that increases the predictability of regulatory oversight would be a welcome change. Another important dimension to the problem is reimbursement, so more clarity around the reimbursement process would also stimulate the development process.

Question 3. In our last hearing, Dr. Hamburg said that the FDA had a record number of new drug approvals last year, touted the success of the Breakthrough therapies program, and told us that FDA's review times for drugs is fastest in the world.

From her statement:

> "This past calendar year, FDA approved 51 novel drugs and biologics, the most in almost 20 years. Today, FDA's average drug review times are consistently faster than other advanced regulatory agencies around the world, providing Americans earlier access to new, innovative drugs than patients in any other country. In achieving these outcomes, FDA has maintained its commitment to high standards to protect the public health, while also exercising regulatory flexibility in order to help promote medical product development. This flexibility, along with FDA's work to collaborate with industry, has helped reduce product development and review times. As a result, Americans are seeing more products being approved, and in many cases, they have access earlier than patients anywhere else in the world."

Could each of you briefly discuss your thoughts on what she said, FDA's performance, and where Congress could be helpful?

Answer 3. Please see previous answer on regulatory uncertainty and the need to reduce it to increase investment in the medical innovation sector.

Question 4. Could you each talk about how the role of the patient has changed with new technology, and what policy changes need to be made to use this new excitement and involvement of patients to move technologies from discovery through development more quickly?

Answer 4. As I discussed in my testimony, the information age and the age of precision medicine are now upon us. Laboratory developed tests that predict patient outcome based upon personalized Omics information will revolutionize how care is delivered and developed in this United States in the coming years. Thus the patient and his/her personal information and individual needs will become increasingly central to medical care as we move the next generation of medical innovations to the public. This new direction poses a lot of challenges for the way we think about oversight. Also, as big data becomes a bigger part of medical care, there are a number of regulatory issues that are raised because computers analyzing datasets are increasingly part of the medical supply chain. This has typically not been something under the purview of the FDA. The Congress together with the FDA need to develop policies that will facilitate the proper use of such information so that it delivers precise medicines to patients as safely and rapidly as possible as well as informs the next round of discovery science and innovation to accelerate the invention and development of future breakthrough medicines and therapies.

SENATOR ISAKSON

Question 1. I understand that some medical device companies have had challenges with the inconsistency and lack of predictability of the FDA inspection process. Can you clarify if and how this can impact innovation?

Answer 1. As indicated above, regulatory uncertainty is perhaps the single biggest impediment to moving innovation to the public. To give some numbers from Dr. Robinson: suppose an investor successfully commercializes one out of every five investments, and suppose they need to earn a 15 percent return on average, including the failed investments, in order to continue to raise new funds. If they expect to invest 5 years before exiting, they need to earn 10x their initial investment in the successful investment in order to generate a 15 percent return on average. If the holding period of the investment goes from 5 years to 8 years, then they have to earn 15 times their investment instead of 10 times their investment in order to earn 15 percent on average. Thus, uncertainty over the time it will take to take products to market completely undermines the economics of investing in biomedical innovation.

Question 2. A number of stakeholders, including public health groups, infectious disease doctors, venture capital, and antibiotic developers to support the PATH Act, legislation sponsored by Senator Hatch and Senator Bennet. This bill would require FDA to create a new, limited population approval pathway for antibiotics to treat serious and life-threatening infections for which there are few or no other treatments. The bill would allow FDA to approve these drugs on the basis of smaller amounts of data than it uses to approve other antibiotics. Can you explain how FDA can use this pathway to get drugs to patients who really need them without lowering the approval standards?

Answer 2. Unfortunately this is out of our area of expertise. However strategies that accelerate FDA approval without lowering standards would clearly encourage investment and accelerate development of therapeutics across a wide range of life threatening diseases.

SENATOR COLLINS

Question. Dr. Sullenger, I am always struck by statistics such as the one you mention in your testimony, that "with a 20 percent decline in the purchasing power of the NIH budget over the past decade," it has become increasingly challenging to create a path to move medical innovations from bench-side findings into bedside interventions for patients. As the Chairman of the Special Committee on Aging, I know the annual cost of caring for Alzheimer's patients is $226 billion, yet we are spending less than three tenths of 1 percent of that amount—less than $600 million a year—on research.

Would you expand on your comments about the importance of training and expanding the next generation of the Nation's biomedical research workforce—including whether you see a correlation between reductions in NIH funding and talented young researchers being discouraged from the field of biomedical research or leaving the country to conduct their research?

Answer. Senator Collins, the statistics that you cite regarding cost for caring for Alzheimer's patients versus spending on Alzheimer's research is remarkable and unfortunate. I have heard similar statistics for the cost of treating stroke patients and the amount spent on stroke research and it is always disheartening to researchers like me who spend their lives trying to understand the causes of disease in an attempt to create novel therapies to reduce suffering and improve health. Our current approach to managing the costs of Alzheimer's, stroke and other diseases is analogous to having a patient hemorrhage and giving them multiple blood transfusions, which he/she will in turn bleed out, rather than researching the cause of problem and stopping the bleeding. As a biomedical scientist, it is difficult for me to understand this approach to healthcare economics as I naturally focus upon the root cause of problems to try to address them. If you and Congress can refocus resources on the cause of disease, I believe that it is the surest way to cost effectively address the medical needs of and improve the lives of our Nation's citizens.

Regarding your question about how the 20+ percent reduction in NIH purchasing power has impacted the next generation of the Nation's biomedical workforce, I would say that I see the negative effects of this almost daily. I have had trainees leave the United States to work in Korea, India and Germany in the last few years and several others that are interested in moving to these countries or others that are investing heavily in biomedical research. Most other trainees, who want to stay in the United States, now prefer to leave academia and work in the private sector if possible because they believe that the current NIH funding environment will not allow them to have a career in academic biomedical science. This situation is a dramatic change from only a few years ago when the best and brightest biomedical trainees all wanted to work in the United States. In addition, I would say that institutions such as mine are also moving parts of their research programs to other countries. Duke University recently started a Medical School in Singapore (*https://*

www.duke-nus.edu.sg) and very recently opened a new campus in China (*http://dku.edu.cn*). Many other universities are doing the same as they try to position themselves for a changing world where Asian countries invest heavily in the pursuit of biomedical knowledge while the United States curtails such investment.

SENATOR WHITEHOUSE

Question. We've heard several stakeholders express support for integrating patient perspectives in the drug development and review process. As you know, FDA held 20 public meetings to consider different disease areas as part of its Patient-Focused Drug Development program. What next steps would you like to see FDA take in its Patient-Focused Drug Development program? Do you have specific recommendations on how FDA could better integrate patient perspectives in the development and review processes?

Answer. Please see response to Chairman Alexander's question 4 above.

EDWARDS LIFESCIENCES LLC,
IRVINE, CA 92614,
April 29, 2015.

Hon. LAMAR ALEXANDER, *Chairman*,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
428 Dirksen Senate Office Building,
Washington, DC 20510.

DEAR CHAIRMAN ALEXANDER: Thank you for the opportunity to testify before the Senate Committee on Health, Education, Labor, and Pensions on March 24, 2015 at the hearing entitled "Continuing America's Leadership: Advancing Research and Development for Patients."

Attached are my responses to the committee's additional questions for the record. Please contact me if there is any further followup. Thank you, again, for the opportunity to participate in this important initiative focused on addressing the challenges in getting cutting edge innovations to patients.

Sincerely,

MICHAEL A. MUSSALLEM,
Chairman and Chief Executive Officer.

RESPONSE TO QUESTIONS OF SENATOR ALEXANDER, SENATOR ISAKSON, SENATOR COLLNS AND SENATOR WHITEHOUSE BY MICHAEL A. MUSSALLEM

SENATOR ALEXANDER

Question 1. There are more than 6,500 medical device companies in the United States, of which 80 percent of the companies have 50 or fewer employees. Has FDA improved the quality and frequency of its communications in the past 2 years that supports the range of innovative medical device companies?

Answer 1. ***Yes. Our experience over the past 2 years has improved***, as FDA has worked with industry to improve the quality and frequency of its communications to support all innovative medical device companies—including those considered "small."

The ability to have frequent, quality discussions with FDA leadership and reviewers—followed by actionable results by both FDA and industry—will continue to improve the regulatory environment for all stakeholders and allow innovative technologies to quickly reach the patients that need them most. Below are examples of programs and organizational efforts that are helping the agency continue to improve its communication with companies.

- Dr. Shuren and his team at FDA have outlined strategic priorities to strengthen the clinical trial enterprise, FDA included as part of its 2014–15 Strategic Priorities a focus on providing excellent customer service, which leverages the use of a standardized survey tool in emails and on the Center's website.
- Thanks to the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA has the resources to improve review and approval performance metrics—including the number, quality and timing of interactions with companies. These metrics are tied to dramatic increases in manufacturer user fees, and we are just beginning to see positive trends in performance.
- A program was established focusing on improving quality and performance, which included corrective and preventive action (CAPA) processes. The industry has

reported that reviewers have reached out directly to companies requesting honest and constructive feedback with regard to FDA performance.

• CDRH has supported the U.S. Submission Advancement Program, an initiative established through the small company division of our trade association, the Advanced Medical Technology Association (AdvaMed) used to gauge industry and FDA performance as it relates specifically to small companies.

• Through several meetings between small company executives and CDRH leadership in 2014, FDA provided useful feedback on common mistakes observed in sponsor submissions, which is facilitating the development of a best practices document that includes an outline of the most frequent mistakes observed by the agency.

• CDRH holds an annual Regulatory Education for Industry (REdI) collaborative conference for small businesses with CDER, allowing such companies the ability to network, engage with FDA experts, and learn more about FDA's regulatory requirements for drugs and medical devices, free of charge.

• CDRH has also established the Experiential Learning Program (ELP), which provides a formal training mechanism for premarket review staff to visit research, clinical, manufacturing, and health care facilities to observe firsthand how medical devices are designed, developed, and utilized.

• CDRH's Office of Communication and Education reorganized in 2014. This reorganization allowed for the Division to focus more heavily on educating all CDRH stakeholders by providing understandable, accessible, science-based regulatory information.

• CDRH has also provided reviewers and leadership the opportunity to engage directly with companies in informal industry settings upon request. Roundtables including participants from industry and CDRH have been organized as "assimilation exercises" to encourage productive conversations around what the agency and industry are doing well—and also areas for improvement.

Question 2. Your company has experience using postmarket registries to help get your innovative product to market. Could you talk about that experience, what worked, what has not worked, and what role you think better data after approval can have in helping new, innovative technologies get to patients faster?

Answer 2. ***Edwards Lifesciences supports appropriate data collection for TAVR patients.*** We generated a substantial amount of clinical evidence to support the safety, efficacy, necessity and reasonableness of the Edwards SAPIEN transcatheter aortic heart valve, including a large, complex, randomized and controlled clinical trial in the United States. Extensive study of this valve—including an unprecedented four New England Journal of Medicine papers—has demonstrated the "triple win": a substantial and sustainable clinical benefit, extraordinary quality-of-life improvement, and cost effectiveness in inoperable patients. In fact, the SAPIEN valves are the most studied heart valve in history, with more than 300 peer-reviewed, published articles on clinical outcomes associated with the valves. There are also more than 120 cost-effectiveness and quality of life articles related to transcatheter aortic valve replacement (TAVR). Subsequent indications and different access routes (used when a direct percutaneous approach is not possible) for SAPIEN were studied in registries, and we conducted a second large trial in the United States—PARTNER II—for SAPIEN XT, a much improved and lower profile device that was approved by FDA in June 2014. Accompanying these large randomized trials have been cost effectiveness and quality of life studies supporting the value of the SAPIEN family.

Edwards provides significant support for the TVT Registry. Following FDA approval and the Medicare National Coverage Decision (NCD) that provided reimbursement for TAVR through Coverage with Evidence Development (CED), the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC) created the TVT Registry, which is designed to monitor and benchmark patient safety and real-world outcomes related to the TAVR procedure.

The TVT Registry has proven to be useful. Our experience with the TVT registry underscores that well-executed registries are a useful postmarket tool. The data from the TVT Registry for transcatheter aortic valve replacement procedures was used by FDA in 2013 to help expand the indications for use of our SAPIEN technology, allowing access to a broader patient population. Through close collaboration between FDA and CMS, when new patient populations are approved, they are immediately covered by Medicare. This collaboration takes vision and commitment by both FDA and CMS, and they should be commended for their work. We think that these novel approaches reflect agency views that take promotion of public health as seriously as they take patient protection, which as consumers of the system, we should all welcome.

The burden and cost of complying with registry requirements is not insignificant. For example, the patient data registry form for the TVT Registry for TAVR procedures is 8 pages long and consists of more than 300 separate fields, requiring special staffing, and dedicated personnel, and hours of work to complete this exhaustive form. Many physicians have told us that it takes longer to fill out the TVT Registry form than it does to perform the TAVR procedure. In addition to the significant financial commitment manufacturers must make to support the development and ongoing operations of registries, hospitals are charged ongoing fees to participate.

Question 3. In 2014, FDA proposed a new voluntary expedited access program intended to speed development and approval of devices that treat or diagnose a life-threatening or debilitating disease and fulfill an unmet medical need. How will this program help you? What additional tools does FDA need to help keep up with the range of new science?

Answer 3. ***FDA's proposed Expedited Access Program is very promising.*** While we are still evaluating how FDA's recently released final guidance on its Expedited Access Program (EAP) could be implemented for products in development, we are encouraged and commend the agency for its efforts to explore supplementary review pathways to provide more timely patient access to new technologies for life-threatening or irreversibly debilitating diseases that address an unmet medical need.

We look forward to working with Congress, FDA, CMS and other stakeholders on ways to implement this proposal and others designed to expedite patient access to safe and effective medical technologies. As part of its Innovation Agenda, ***AdvaMed has proposed a new breakthrough pathway, which builds upon FDA's EAP and would provide for transitional Medicare and Medicaid coverage for products designated and approved by FDA as "breakthrough."***

Question 4. We do not want to waste time this year, and want to focus on the areas that have the greatest impact on improving our biomedical research enterprise? What are the two or three things that, if done right, would help you accomplish your goals?

Answer 4. ***FDA's vision to improve the regulatory process is commendable, and we believe it must be accelerated.*** There are a number of regulatory reforms, included in the AdvaMed Innovation Agenda, which would lead to greater efficiency and consistency in the FDA medical device review process.

To encourage innovation, we need to address issues throughout the entire ecosystem. ***A true innovation agenda must address both FDA and CMS,*** and we urge this committee and the Senate Finance Committee to consult with each other as you move forward to find ways to promote innovation.

The breakthrough pathway is one of the most important proposals in the innovation agenda; it spans the jurisdiction of both committees and can only be enacted effectively through a cooperative effort.

Question 5. In our last hearing, Dr. Hamburg said that the FDA had a record number of new drug approvals last year, touted the success of the Breakthrough therapies program, and told us that FDA's review times for drugs is fastest in the world.

From her statement:

> "This past calendar year, FDA approved 51 novel drugs and biologics, the most in almost 20 years. Today, FDA's average drug review times are consistently faster than other advanced regulatory agencies around the world, providing Americans earlier access to new, innovative drugs than patients in any other country. In achieving these outcomes, FDA has maintained its commitment to high standards to protect the public health, while also exercising regulatory flexibility in order to help promote medical product development. This flexibility, along with FDA's work to collaborate with industry, has helped reduce product development and review times. As a result, Americans are seeing more products being approved, and in many cases, they have access earlier than patients anywhere else in the world."

Could each of you briefly discuss your thoughts on what she said, FDA's performance, and where Congress could be helpful?

Answer 5. While I cannot speak to the drug review process and performance, on the device side, FDA is pursuing initiatives to improve the regulatory processes to help patients access innovative therapies. Thanks to the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA has agreed to improved review and approval performance metrics tied to dramatic increases in manufacturer user fees,

and we are just beginning to see positive trends in performance. However, it remains the case that companies' experiences with the FDA device review process are largely reviewer-dependent.

Question 6. Could you each talk about how the role of the patient has changed with new technology, and what policy changes need to be made to use this new excitement and involvement of patients to move technologies from discovery through development more quickly?

Answer 6. ***FDA has pursued a number of relatively new initiatives which we hope will improve patient involvement as they get put into practice.*** Edwards Lifesciences and our trade association, AdvaMed, support efforts to improve patient involvement in the product development and review process. We believe patients have an important role in making benefit-risk determinations when it comes to their care. Both FDA and industry need to work to ensure that these initiatives are implemented in a way that maximizes patient access to safe and effective technologies.

FDA has engaged in a commendable effort to involve patients and incorporate their perspectives into the regulatory process. Specifically, FDA has issued two guidance documents intended to address patient perspective of benefit and risk.[1] These documents address how patient-centered outcomes can and should be included in clinical trials of certain devices and how FDA should incorporate these endpoints in their review of the supporting evidence for a device. Further, FDA and the Medical Device Innovation Consortium are also working on models to quantify the patient perspective, and when during the product lifecycle such input should be sought/provided.

In addition, pursuant to the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA seeks to solicit patients' as well as other stakeholders' (*e.g.*, surgeons, other health care professionals, and caregivers) perspectives and participation throughout the total product life cycle (TPLC) of medical devices, including regulatory decisionmaking. It is important to recognize that each patient has a unique benefit-risk perspective based on their own particular situation, and that patients are heterogeneous even within a single disorder (*i.e.*, there is no "representative patient").

There exists some concern that adding an additional regulatory requirement to an already cumbersome process could negatively impact patient access to new technologies. In some cases, there are devices/therapies that do not lend themselves to patient input at all phases of the TPLC (*e.g.*, devices with no patient interface). Surgical devices, for example, are designed to aid the surgeon in the safe use and/or application of the device for the benefit of the patient. Therefore, patient input on device design and clinical trials should not be an absolute requirement for medical device manufacturers. We believe that it is appropriate and necessary in some cases for patient "surrogates," such as physicians, surgeons, or other health care providers, to provide input, especially at the early stages of device design/development.

SENATOR ISAKSON

Question 1. I understand that some medical device companies have had challenges with the inconsistency and lack of predictability of the FDA inspection process. Can you clarify if and how this can impact innovation?

Answer 1. Inconsistency and lack of transparency and predictability of the FDA inspection process can have a substantial impact on innovation and the timing of device development and approval. ***This is an important issue to our industry and we encourage the committee to examine the process and what improvements could be made to the inspection process***.

Specifically, there is inconsistency in investigators' knowledge and interpretation of the Quality System Regulation (including the interpretation of risk) and inspection protocols, both domestic and abroad, and also among field offices domestically. These problems hamper the ability to assure ongoing and mutual understanding between FDA and industry of what is required by regulation, which is essential to achieving high rates of compliance, ultimately leading to the quicker approval of safer and higher quality medical devices.

FDA's efforts to improve its regulatory management processes and structure through the recommendations coming from its Program Alignment Group are an im-

[1] "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics Draft, July 2014]" and "Guidance for Industry and Food and Drug Administration Staff—Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" [Final, March 2012].

portant step in the right direction. It would be worthwhile for Congress to spend time assessing how to best move this process forward.

As noted above, these challenges with the inspection process are of great interest to the industry and in an effort to help identify and address the issues, AdvaMed has established a working group focused on the issue of inspections and create opportunities to collaborate with FDA and Congress to improve the consistency, predictability, and transparency of the inspection process.

Question 2. A number of stakeholders, including public health groups, infectious disease doctors, venture capital, and antibiotic developers to support the PATH Act, legislation sponsored by Senator Hatch and Senator Bennet. This bill would require FDA to create a new, limited population approval pathway for antibiotics to treat serious and life-threatening infections for which there are few or no other treatments. The bill would allow FDA to approve these drugs on the basis of smaller amounts of data than it uses to approve other antibiotics. Can you explain how FDA can use this pathway to get drugs to patients who really need them without lowering the approval standards?

Answer 2. As a medical device company, we do not have a perspective on the drug approval pathway.

SENATOR COLLINS

Question. Mr. Borisy and Mr. Mussallem, you both mentioned in your written testimonies the need to strengthen and integrate patient perspectives. The patient perspective in the drug development and review process is something I am hearing more about from individuals and families who are suffering from devastating diseases.

Particularly in areas of serious unmet medical need, how does the patient voice and understanding the benefits and risks to a patient help ensure that medical innovations are helping to meet patients' needs?

Answer. ***FDA has pursued a number of relatively new initiatives which we hope will improve patient involvement as they get put into practice.*** Edwards Lifesciences and our trade association, AdvaMed, support efforts to improve patient involvement in the product development and review process. We believe patients have an important role in making benefit-risk determinations when it comes to their care. Both FDA and industry need to work to ensure that these initiatives are implemented in a way that maximizes patient access to safe and effective technologies.

FDA has engaged in a commendable effort to involve patients and incorporate their perspectives into the regulatory process. Specifically, FDA has issued two guidance documents intended to address patient perspective of benefit and risk.[2] These documents address how patient-centered outcomes can and should be included in clinical trials of certain devices and how FDA should incorporate these endpoints in their review of the supporting evidence for a device. Further, FDA and the Medical Device Innovation Consortium are also working on models to quantify the patient perspective, and when during the product lifecycle such input should be sought/provided.

In addition, pursuant to the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA seeks to solicit patients' as well as other stakeholders' (*e.g.*, surgeons, other health care professionals, and caregivers) perspectives and participation throughout the total product life cycle (TPLC) of medical devices, including regulatory decisionmaking. It is important to recognize that each patient has a unique benefit-risk perspective based on their own particular situation, and that patients are heterogeneous even within a single disorder (*i.e.*, there is no "representative patient").

There exists some concern that adding an additional regulatory requirement to an already cumbersome process could negatively impact patient access to new technologies. In some cases, there are devices/therapies that do not lend themselves to patient input at all phases of the TPLC (*e.g.*, devices with no patient interface). Surgical devices, for example, are designed to aid the surgeon in the safe use and/or application of the device for the benefit of the patient. Therefore, patient input on device design and clinical trials should not be an absolute requirement for medical device manufacturers. We believe that it is appropriate and necessary in some cases for patient "surrogates," such as physicians, surgeons, or other health care providers, to provide input, especially at the early stages of device design/development.

[2] Ibid.

SENATOR WHITEHOUSE

Question. We've heard several stakeholders express support for integrating patient perspectives in the drug development and review process. As you know, FDA held 20 public meetings to consider different disease areas as part of its Patient-Focused Drug Development program. What next steps would you like to see FDA take in its Patient-Focused Drug Development program? Do you have specific recommendations on how FDA could better integrate patient perspectives in the development and review processes?

Answer. While the Patient-Focused Drug Development program is limited to drugs, there are a number of activities that FDA's device center is undertaking, with support of the medical device industry, to incorporate the patient perspective. ***FDA has pursued a number of relatively new initiatives which we hope will improve patient involvement as they get put into practice.*** Edwards Lifesciences and our trade association, AdvaMed, support efforts to improve patient involvement in the product development and review process. We believe patients have an important role in making benefit-risk determinations when it comes to their care. Both FDA and industry need to work to ensure that these initiatives are implemented in a way that maximizes patient access to safe and effective technologies.

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RESPONSE TO QUESTIONS OF SENATOR ALEXANDER, SENATOR ISAKSON, AND SENATOR WHITEHOUSE BY ALLAN COUKELL

SENATOR ALEXANDER

Question 1. You mention in your testimony that the cost of doing clinical trials in the United States is greater than that in other countries in a few specific cases. Could you expand on what we could do to make trials here more efficient?

Answer 1. The rising cost of medical product innovation is a serious concern with multiple underlying causes, including expenses associated with clinical trials. The data researchers collect through robust trials are critical for regulators, payors, clinicians, and patients to make decisions about which products are right for which patient. A 2013 survey found that phase III clinical trial costs rose by 86 to 88 percent over 3 years—from $25,000 to $40,000 per patient. While Pew has not conducted a comprehensive analysis on the cost of clinical trials, we have identified some strategies—including those used abroad—to reduce the costs of clinical trials.

Clinical trial experts have proposed other approaches that can reduce study costs and facilitate innovation. For example, the Institute of Medicine convened experts who proposed several solutions to reduce trial costs, including the development of "large, simple trials," where study investigators would enroll many patients but only examine a small number of variables.

One source of cost in any trial is the number of data elements that are collected. Another approach to reducing trial costs involves "large, simple trials."[1] Such trials have the potential to reduce costs by simplifying eligibility criteria and reducing the number of outcomes tracked. No statutory or regulatory barrier precludes adoption of such trial designs. Rather, a participant in an IOM workshop described the barrier as "risk aversion . . . "

> "Researchers may believe that it is better to collect 100 unnecessary variables than to miss one important one. Additionally, Granger explained, regulatory departments and contract research organizations have a substantial financial stake in maintaining the status quo, as their business models and margins are created by the complexity inherent to current trial designs. Last, the lack of international harmonization among trial designs can force the use of the most complicated common denominator."[1]

One approach to large simple trials is the registry-based trial. Registries are large data bases that contain detailed clinical information on patients with similar medical conditions. Researchers in Sweden used a registry to conduct a large cardio-

[3] Ibid.

vascular trial at a fraction of the per-patient costs. The TASTE trial enrolled more than 7,000 patients, and allowed investigators to keep track of every patient throughout the course of the research at a total cost of $50 per patient, or only $300,000 for the entire trial. Conducting a traditional study of this size in the United States would cost tens of millions of dollars, if not more.

Pew, together with the Blue Cross Blue Shield Association and the Medical Device Epidemiology Network, convened experts from the medical device industry, the registry community and government to consider how to achieve the full potential of registries in a financially sustainable way. Several barriers exist to fully achieving the promise of registries. Despite the dramatic uptake of electronic health information sources, these systems cannot easily transmit data among one another. This lack of interoperability, for example, hinders the ability of registries to extract clinical and outcomes data from EHRs. Instead, registries must build customized solutions to extract information from the EHR systems at each facility, or require providers to manually enter the information. Additionally, many registries have sought clarity on when their studies are considered research, rather than quality improvement efforts. This confusion has slowed their use by hospitals and their ability to make a meaningful contribution.

While the use of registries can supplement existing efforts to reduce costs, they are not appropriate for all products or studies. Other strategies to help address trial costs include facilitating faster trial initiation through, for example, greater use of central institutional review boards (IRBs) instead of multiple local reviews. For medical devices in particular, trials are currently required by statute to obtain IRB review at each facility participating in a study.[2] Removing this requirement could help streamline the approval of these trials.

The growth in trial size is driven in part by the effect size of the drug. When a drug's effect can only be discerned by studying it in thousands of patients, the clinical trials required for approval will necessarily be large. A treatment that worked in 100 percent of patients, by contrast, would require an extremely small clinical trial. As Scannell *et al.* note,

> "everything else being equal, clinical trial size should be inversely proportional to the square of the effect size. If the effect size halves, the trial has to recruit four times as many patients to have the same statistical power."[3]

Personalized, or precision, medicine has the potential to identify sub-populations of patients with specific genetic profiles who are more likely to respond to a particular therapy. This has the potential to reduce trial size if the response rate is high (as with any drug). However, it is important to note that if the response rate is low and seen only in a specific sub-population, the usual challenges of clinical trial design and recruitment will be further exacerbated.

Innovative trial designs and novel partnerships have the potential to more efficiently recruit and stratify patients by genetic profile. The FDA has encouraged the development of such trials. For example, the recently developed Lung-MAP trial has the potential to improve efficiency by allowing simultaneous and sequential comparisons of multiple drugs (from multiple companies) and stratification of patients by genotype.[4] Such a trial still involves a 1:1 randomization of patients that does not change in response to data analysis, and is therefore not of Bayesian or adaptive design.

While adaptive trials may under some circumstances improve trial efficiency, it is important to note that—contrary to widely held perceptions—such trials do not reduce the number of participants required to achieve adequate power (and can, under certain circumstances, increase it).

Question 2. Pew conducted surveys on how to define and improve predictability with the regulatory process. What did those surveys find would be most helpful in reducing the uncertainty of medical product development?

Answer 2. Through a series of activities, Pew sought to better define what is perceived as unpredictability in FDA's regulatory review process and to identify concrete steps that the FDA and sponsors could take to improve predictability. Pew staff reviewed relevant peer-reviewed journal articles and other publicly available documents, interviewed more than two dozen individuals, including representatives from small and large drug and device companies, former FDA officials, consultants, venture capitalists, and patient advocacy groups and held a 1-day public workshop attended by leaders from the FDA, the drug and medical device industry, the venture capital community and other stakeholders. We also fielded a survey of senior drug, biotechnology and device company executives (randomly selected from a master list that was compiled to be as comprehensive as possible), assessing their perceptions and experiences concerning the predictability of FDA's regulatory review.

Of the 210 drug and device industry professionals polled, about 70 percent said the FDA makes the appropriate decision on new medical products "most or all of the time" and 66 percent said FDA staff's qualifications are "excellent or good." About 62 percent of the respondents said FDA's data requirements are necessary in "all or more cases," with only 2 percent saying the requirements were necessary in "very few cases."

Almost all of the survey respondents—98 percent—agreed on the importance of predictability in the FDA review process. Eighty-one percent said it was "extremely important" and another 17 percent said it was "fairly important" for the FDA review process for new medical products to be predicable.

When probed further, most respondents to the survey as well as workshop participants expressed concerns regarding the agency's predictability. Thirty-eight percent of industry respondents said, based on their personal experiences, that the FDA's regulatory review process is "completely or fairly" predictable (48 percent among biotechnology and pharmaceutical professionals). Only 26 percent of medical device professionals said the same, which reflected an overarching pattern of greater dissatisfaction within that industry. (Pew did not explore this discrepancy in its quantitative research, but some participants in the January 2013 conference attributed the difference to the greater diversity of medical devices compared to pharmaceutical products and the subsequent breadth of approaches to testing their safety and efficacy, as well as staffing issues within CDRH, which the division acknowledged.)

Sixty-eight percent said that such unpredictability discouraged the development of new products. Again, a higher proportion of medical device professionals—84 percent—believed that the FDA's review process discouraged innovation.

Industry professionals were divided on the degree to which they believed the system needs to be fixed. Nearly half (49 percent) believe the agency's product review systems need a "complete or major overhaul." The same number said the systems worked "fine as-is" or needed only "minor modifications."

One clear theme emerged from the Pew conference and related activities: Regulatory predictability is a broad and subjective term used to describe a variety of issues. Therefore, attempts to solve "regulatory predictability" are less likely to succeed because the problem itself is not defined precisely enough. Rather than relying on this broad diagnosis, stakeholders would be better served to articulate specific issues regarding, for example, communications, staff experience, or data accessibility. Those identified during the course of our research include:

- Establishing clear data requirements;
- Inconsistency among FDA reviewers and review divisions;
- Issues related to the publication of guidances;
- Data integration and accessibility; and
- Sponsor inexperience with regulatory review.

Establishing Clear Data Requirements

Sponsors assert that there is often a lack of clarity or explicit rationale regarding the type and quantity of additional safety and efficacy data that FDA staff requests. Specifically, several sponsors asserted that such requests are manifestations of an inherent and unwarranted "risk-aversion" on the part of FDA staff. As they submit documents to the agency, FDA staff will request additional information to address possible concerns with a product or learn more about how a drug will affect patients. Sponsors contend that many of these data requests would negligibly affect FDA's decisions but are burdensome and expensive. Similarly, they assert that some data requests are too academic and not germane to the safety and efficacy of a product.

Current and former FDA officials contend that the FDA must maintain some measure of flexibility when evaluating sponsors' applications. Over the course of a product's lifecycle new information may become available—from the scientific literature, from its regulatory counterparts in other jurisdictions, among other places—that compels the FDA to look at a sponsor's application in a new light. Moreover, in the course of reviewing applications from other sponsors on a similar product, and through post-marketing surveillance monitoring, FDA reviewers identify potential safety and efficacy issues with a product class and uses that information to make additional data requests of sponsors. Because specific reference to other sponsor's applications is prohibited by commercial confidentiality laws, FDA staff cannot always be specific about the reasons underlying a particular data request, leading to sponsor perceptions of FDA capriciousness or arbitrariness.

To achieve greater predictability, our conference found substantial—though not universal—support for the suggestion that the FDA should release all documents—such as Complete Response Letters—that would provide information on why the

agency requested additional information. That information will help all companies understand the data sought for certain diseases and about classes of medical products.

We also found strong support for investments in regulatory science so that the agency can develop tools, standards, and approaches to product reviews that can provide some consistent guidance for sponsors even as science itself advances.

Some sponsors expressed concerns that the FDA did not order Risk Evaluation Mitigation Strategies (REMS)—which implement controls to help prevent the harmful effects of new medicines—until very late in product review. Discussing REMS late in product reviews delays drug approvals as the sponsor and FDA reach an agreement on the post-market safety program. Earlier REMS planning would streamline approvals, though it must be noted that at least some of the time, REMS development will be in response to risk information obtained in phase III trials—data the FDA does not have an opportunity to review until the full application is submitted.

As part of the new review model for new molecular entities and original biologics license application, the FDA will begin discussing REMS and other risk-related issues much earlier in product reviews and even during meetings before the formal submission of an application. The FDA has also formalized several mid-cycle communications—including both in-person meetings and letters from the agency—to provide more interactions between reviewers and drug sponsors for the agency to provide feedback.

CDRH has created a new Innovation Pathway, where device sponsors and reviewers interact throughout product development to address any potential FDA concerns before manufacturers formally submit a product for review.

Inconsistency Among Reviewers and Between Review Divisions

Ensuring the safety, effectiveness, and quality of human drugs for these products is a complicated regulatory task, requiring FDA's consideration of a multitude of complex factors. FDA's regulatory decisionmaking process takes into consideration not only the data submitted for a particular marketing application, but also a broad set of additional factors, including similar products in a class, clinical context for the proposed product (such as the nature and severity of the disease or condition that the proposed product is intended to treat or prevent and the benefits and risks of other available therapies for that disease or condition) and any risk management tools that might be necessary to ensure that the benefits of the proposed product outweigh its risks.

The complexity described above is sufficient to drive some degree of inconsistency in regulatory decisionmaking among reviewers and review divisions. A drug with apparent cardiotoxicity might require investigations that a pharmacologically similar product without that safety signal did not. The risk tolerance for uncertainty for an antibiotic to treat a multidrug resistant infection might be different than for a drug intended as a first-line treatment. However, there are a host of other internal and external variables that also drive this inconsistency, including: the number of regulatory filings (workload); division staff levels; frequency of Advisory Committee meetings; requests for REMS or other post-marketing commitments; and the variable quality of the sponsors' applications.

In addition to these differences between review divisions, differences among reviewers may feed sponsor perceptions of inconsistency. Judgments about balancing risks and benefits are inherently value judgments, and such differences among reviewers are, to a certain degree, inevitable. The FDA should not necessarily eliminate such differences, but instead should put in place processes and tools that make these differences transparent and subject to discussion—at higher levels within the agency, with sponsors, and, where appropriate, with the public.

Most of the survey respondents attributed these challenges primarily to staffing shortages. Sixty percent said FDA did not have sufficient scientists and reviewers to conduct timely product reviews. In fact, respondents who were satisfied with FDA processes were more likely to say that FDA was insufficiently staffed.

More tractable may be inconsistencies among reviewers that are attributable—at least in part—to a lack of training. Not all reviewers are well-versed on agency policies and guidances. Therefore, one participant suggested, reviewers occasionally provide inconsistent advice to sponsors—such as whether an adaptive trial design is viable—that may not reflect guidance or direction from FDA leadership.

Most respondents (54 percent) suggested that investing in human resources, such as training staff, would be a "very effective" strategy for improving FDA's review process. An additional 26 percent said it would be "fairly effective," making it the most popular proposal offered in the survey.

As required by Congress, the FDA has sought to make the rationales for reviewer judgments more transparent through the implementation of a structured risk-benefit framework for NDAs and BLAs. Through this framework, reviewers will explain product risks along with whether the drug treats an unmet need or provides major advancements to patient care. Including this framework earlier in product development could improve FDA decisionmaking. Stakeholders expect this new framework to serve as a communications tool to explain FDA decisions as well as to provide a quick summation of a review to help cross-agency consistency on what review decisions were made. FDA's device center has also issued a guidance document outlining its benefit-risk framework. To evaluate benefits, FDA examines the clinical improvements, magnitude of benefits, probability of the patient experiencing the benefit and the duration of the effect. For safety, FDA evaluates the serious and non-serious adverse effects and procedure-related complications (such as the probability and duration of harmful events or the risk of false results from diagnostics).

The FDA has contracted independent third parties to examine its review processes and communications with sponsors. The reviews should identify areas where the FDA is inconsistent and not following good review practices.

When meeting with the FDA about adaptive trial designs or other issues that are not typical for a standard drug application, sponsors should request the attendance and input of senior FDA leadership. Such input could provide needed reassurance to reviewers and assuage their concerns with a product review.

The FDA should provide additional and ongoing training for product reviewers, with a focus on developing and implementing guidances.

Issues Related to the Publication of Guidances

Guidance documents are nonbinding recommendations that represent the FDA's current thinking on a particular subject. They are written for multiple audiences, including sponsors, investigators, Institutional Review Boards (IRBs) and FDA staff. Guidances fall into three broad categories: (1) those related to topics that inform product development, such as study design, use of novel technologies, statistical considerations, and labeling and promotion, (2) those related to procedures and processes such as meetings, timelines, submission requirements, and (3) those related to inspections and enforcement. In our research, concern focused largely on the first type of guidance documents. FDA staff, sponsors and other stakeholders all share the view that the timely publication of relevant guidances—in either draft or final form—are important for making the regulatory review process more predictable and transparent. According to the survey, 90 percent of respondents said written guidances related to FDA's procedures and processes were extremely or fairly helpful. Similarly, 73 percent said FDA's written guidances related to scientific topics that inform product development were extremely or fairly helpful. But others were skeptical about the value of additional guidances, noting that the most challenging questions are often product specific.

We identified several key challenges related to guidances. Among them, the FDA lacks the staffing capacity necessary to both write guidances and also keep pace with product reviews. Because these reviews must meet legislatively mandated deadlines, the FDA prioritizes them, occasionally at the expense of guidance development. A senior FDA official noted that the FDA staff viewed as the most capable of writing guidance documents (regulatory experience, scientific expertise, writing skill) are frequently the highly skilled reviewers. As a result, there is reluctance to explicitly curtail their product review duties in order to devote time to guidance writing.

Data Integration and Accessibility

Drug development—from earliest discovery through post-marketing—is a complex enterprise that generates reams of preclinical and clinical data. For data to be marshaled as evidence requires approaches and tools that systematically facilitate: (1) data integration and (2) data accessibility. With regard to integration, there is a need for standardized data submissions to be the norm, not the exception. Such standards allow for data—clinical and nonclinical—from numerous applications to be pulled into datasets for comparative or meta-analyses. These analyses would likely improve predictability by enabling meaningful comparisons of similar products.

FDA has also heretofore lacked the capacity to make historical application data readily and routinely available to its reviewers. Rather, some—but by no means all—reviewers try to track down applications of similar products in the archives, or they rely ad hoc on the reviewers of those products (assuming these individuals are available). Moreover, time pressure created by user fee agreements disincentivizes efforts to access this historical data.

The lack of data integration and inaccessibility, combined with the time pressures of review work, means that reviewers may spend the bulk of their time reorganizing the data attached to a particular new application and simply rerunning the analyses submitted by sponsors. While this is a critical first-order task, it forces reviewers to focus almost exclusively on the application in front of them, without regard for the agency's regulatory experience with like products. By treating each new application in a vacuum, there are lost opportunities to foster the organizational learning needed to improve consistency and predictability.

CDER has recently increased its support for standardized study data submissions using CDISC standards, and will continue to do so in the future. CDER's Office of Translational Sciences has recently launched a Computational Sciences Center (CSC), whose mission is to improve the effectiveness of reviewers' evaluation and analysis of nonclinical and clinical study data. CSC views data integration and accessibility as core values, and is currently looking for approaches and tools that can help put these values into the day-to-day practice of drug development and regulatory review, both at the FDA and in industry.

Sponsor Inexperience With the FDA

Inexperience submitting products for FDA review leads to sponsors maintaining inaccurate expectations about data requirements and agency processes, ultimately resulting in perceptions of unpredictability when those expectations are not met. Small companies are especially susceptible to this problem. A study by Booz Allen Hamilton found that large companies obtain approval on their original submission 58 percent of the time, whereas that is true for only 41 percent of small company submissions.[5] More recently, a PriceWaterhouseCoopers survey found that large companies were more likely to avail themselves of interactions with the FDA; smaller companies were more likely to rely on guidance.[6]

Sponsors that have not previously submitted products to the FDA for review may lack an accurate understanding of the data requirements and agency processes. Moreover, many small companies fail to hire experienced consultants and regulatory experts to assist with product submissions. Without this help, companies may submit inadequate or noncompliant submissions to the FDA.

Question 3. We do not want to waste time this year, and want to focus on the areas that have the greatest impact on improving our biomedical research enterprise? What are the two or three things that, if done right, would help you accomplish your goals?

Answer 3. We urge the committee to consider S. 185, the Promise for Antibiotics and Therapeutics for Health (PATH) Act, introduced by Senator Hatch and Senator Bennet. This legislation, which has the support of industry stakeholders, key professional societies, public health groups, and military and veterans' groups, would direct FDA to establish a new regulatory pathway for antibiotics to treat serious and life-threatening infections for which there are few or no other treatment options. This legislation is ripe for consideration given the growing public health crisis posed by antibiotic resistance and the consensus that this pathway could make a difference by encouraging the development of antibiotics to meet serious unmet medical needs. An op ed has been written by Drs. Patty Wright and William Schaffner, both infectious diseases specialists at Vanderbilt University, in support of this legislation.

Question 4. In our last hearing, Dr. Hamburg said that the FDA had a record number of new drug approvals last year, touted the success of the Breakthrough therapies program, and told us that FDA's review times for drugs is fastest in the world.

From her statement:

> "This past calendar year, FDA approved 51 novel drugs and biologics, the most in almost 20 years. Today, FDA's average drug review times are consistently faster than other advanced regulatory agencies around the world, providing Americans earlier access to new, innovative drugs than patients in any other country. In achieving these outcomes, FDA has maintained its commitment to high standards to protect the public health, while also exercising regulatory flexibility in order to help promote medical product development. This flexibility, along with FDA's work to collaborate with industry, has helped reduce product development and review times. As a result, Americans are seeing more products being approved, and in many cases, they have access earlier than patients anywhere else in the world."

Could each of you briefly discuss your thoughts on what she said, FDA's performance, and where Congress could be helpful?

Answer 4. Perhaps the most commonly cited measure of FDA performance is drug approval time. Recent studies have demonstrated that FDA approves drugs more quickly than regulators in Europe and Canada.[7 8] Moreover, median time to approval today is substantially lower than prior to the implementation of PDUFA goals.[9] Over recent decades, the overall success rate for New Drug Applications (NDAs) has been relatively consistent (averaging 79 percent from 1993–2012), but the share of drugs approved at the first action date has increased markedly (45 percent over 20 years, but 77 percent in 2011–12).[10] To a large extent that is a function of the quality of the applications.[5] FDA has some capacity to influence submission quality through its communication with industry, either during individual meetings or through guidance documents. According to a recent PriceWaterHouseCoopers survey of industry executives, 78 percent responded that FDA has improved the quality and frequency of its communications with industry over the last 2 years, and 76 percent responded that the agency provided "actionable feedback."[6]

Other measures provide insights on additional aspects of agency operations, such as presentations to societies, consortia, industry and government organizations (around 100 per month for the center for drugs).[11] Of particular interest may be issuance of FDA guidance documents, which serve to communicate the agency's current thinking on specific topics. The center for drugs, for example, issued 51 draft guidances in 2014, but only 13 final guidances.[12] Earlier years follow a similar pattern. The reasons for this discrepancy are unclear. It may be that the agency seeks a wide range of input during development of a draft guidance, which then serves as an effective tool for communicating with stakeholders. Alternatively, it may be that the process for administrative clearance deters the agency from finalizing guidances. Congress could evaluate the balance between finalizing guidances and the potential opportunity cost of fewer new draft guidances on other topics, and potentially identify administrative simplifications that would facilitate finalization. A similar investigation of the time required to develop and finalize a formal FDA rule (often several years) might lead to solutions that would support greater overall efficiency.

The FDA exhibits substantial flexibility in requirements for evidence to support drug or device approval. For example, an analysis by the National Organization for Rare Disorders found that of 135 drug approvals for non-cancer rare disease, 45 met traditional data requirements, 32 reflected "administrative flexibility" based on a previously documented FDA system, and 58 reflected flexibility applied on a case-by-case basis.[13] Another recent analysis of all drug approvals (funded by Pew) found that while FDA generally relied on randomized clinical trials to approve therapeutics, over one-third of approvals were based on a single efficacy trial.[8] This same analysis also showed that FDA used flexibility with regards to which outcomes these trials had to measure.

Several existing mechanisms provide flexibility for the data collected. The accelerated approval pathway for drugs, which Congress codified into law in 2012, allows FDA approval based on surrogate—rather than clinical—endpoints, with the goal of enabling more efficient premarket studies. In 2014, FDA approved 20 percent of novel new drugs through this pathway.[14]

Similarly, for devices that treat or diagnose conditions affecting fewer than 4,000 patients per year, FDA can also grant a humanitarian device exemption, which allows the marketing of a product that is considered safe and is expected to provide benefits, even if less evidence on effectiveness is available. The FDA's proposed expedited access pre-market approval (EAP) process would also support the marketing of new medical devices based on surrogate endpoints, shorter clinical trials or other adaptive designs. The success of this policy, though, relies on the efficient collection of data—both pre- and post-market. Congress should explore codifying this program in statute, and should address some gaps in FDA's authority to accelerate patient access to new medical devices while still collecting sufficient information throughout a product's entire life cycle. In particular, Congress should assess the agency's ability to promptly remove the approval of devices that ultimately were not found to be safe and effective.

These programs provide FDA with significant latitude to tailor the data collected by sponsors and the agency's review process to reflect the severity of the disease and availability of alternative treatments, not to mention each product's risks and benefits. Not all products are appropriate for inclusion in one of these mechanisms, and FDA should only apply some of the pathways—particularly those that result in less than definitive proof of clinical efficacy—to products that are expected to significantly advance care for patients with serious, unmet medical needs.

Question 5. Could you each talk about how the role of the patient has changed with new technology, and what policy changes need to be made to use this new ex-

citement and involvement of patients to move technologies from discovery through development more quickly?

Answer 5. This is not an area in which Pew has comments.

SENATOR ISAKSON

Question 1. I understand that some medical device companies have had challenges with the inconsistency and lack of predictability of the FDA inspection process. Can you clarify if and how this can impact innovation?

Answer 1. We refer the Senator to our response to Chairman Alexander, above.

Question 2. A number of stakeholders, including public health groups, infectious disease doctors, venture capital, and antibiotic developers to support the PATH Act, legislation sponsored by Senator Hatch and Senator Bennet. This bill would require FDA to create a new, limited population approval pathway for antibiotics to treat serious and life-threatening infections for which there are few or no other treatments. The bill would allow FDA to approve these drugs on the basis of smaller amounts of data than it uses to approve other antibiotics. Can you explain how FDA can use this pathway to get drugs to patients who really need them without lowering the approval standards?

Answer 2. Antibiotic resistance remains a serious patient safety, public health, and national security concern. As a 2014 report by the President's Council of Advisors on Science and Technology (PCAST) noted, the development of antibiotic resistance is occurring at an alarming rate and far outpacing the development of new antibiotics. As a result, increasing numbers of patients are contracting serious and even deadly infections that are difficult and sometimes impossible to treat, resulting in longer hospital stays, complications of other medical treatments such as surgery or chemotherapy, and even deaths. Patients with weakened immune systems, such as those with HIV/AIDS, preterm infants, cancer patients, transplant patients, the elderly, or patients treated in intensive care units are at heightened risk, but even healthy young people are contracting and dying from serious, antibiotic resistant infections.

Antibiotic development has dwindled, with many pharmaceutical companies leaving this market. One key reason has been the lack of a clear, feasible regulatory pathway for Food and Drug Administration (FDA) approval of a new antibiotic for some of the most serious infections caused by multidrug-resistant (MDR) pathogens. It is often not feasible to develop antibiotics for some of the most serious infections using traditional, large clinical trials due to the limited numbers of patients in whom these infections currently occur. PCAST explicitly recommended the creation of a new limited population pathway for antibiotics to treat a serious or life-threatening infection in order to meet an unmet medical need. This is exactly what the PATH Act would do.

Importantly, any drug approved under this new pathway must still meet the Food and Drug Administration's (FDA) standards of evidence for safety and effectiveness for the indicated limited population. Further, the PATH Act contains several important provisions to help guide the appropriate use of antibiotics approved under this new pathway. Appropriate use is critical to deliver optimal patient care while limiting the likelihood of antibiotic resistance developing to these new antibiotics.

SENATOR WHITEHOUSE

Question. We've heard several stakeholders express support for integrating patient perspectives in the drug development and review process. As you know, FDA held 20 public meetings to consider different disease areas as part of its Patient-Focused Drug Development program. What next steps would you like to see FDA take in its Patient-Focused Drug Development program? Do you have specific recommendations on how FDA could better integrate patient perspectives in the development and review processes?

Answer. We do not have a specific recommendation.

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[Whereupon, at 11:26 a.m., the hearing was adjourned.]

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