21ST CENTURY CURES: THE PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY (PCAST) REPORT ON DRUG INNOVATION

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

SECOND SESSION

MAY 20, 2014

Serial No. 113–145

Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE

91–548 PDF WASHINGTON : 2015

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[1] Supporting documents submitted by Mr. Sasinowski are available at http://docs.house.gov/Committee/Calendar/ByEvent.aspx?EventID=102237.

[2] Mr. Tunis did not answer submitted questions for the record by the time of printing.

21ST CENTURY CURES: THE PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY (PCAST) REPORT ON DRUG INNOVATION

TUESDAY, MAY 20, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2322 of the Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Blackburn, McMorris Rodgers, Lance, Cassidy, Griffith, Bilirakis, Ellmers, Barton, Upton (ex officio), Pallone, Engel, Schakowsky, Green, Barrow, Sarbanes, and Waxman (ex officio).

Also present: Representative DeGette.

Staff present: Clay Alspach, Chief Counsel, Health; Gary Andres, Staff Director; Mike Bloomquist, General Counsel; Matt Bravo, Professional Staff Member; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Katie Novaria, Professional Staff Member, Health; Krista Rosenthall, Counsel to Chairman Emeritus; Chris Sarley, Policy Coordinator, Environment and the Economy; Heidi Stirrup, Policy Coordinator, Health; John Stone, Counsel, Health; Ziky Ababiya, Democratic Staff Assistant; Phil Barnett, Democratic Staff Director; Eric Flamm, Democratic FDA Detailee; Elizabeth Letter, Democratic Press Secretary; Karen Lightfoot, Democratic Communications Director and Senior Policy Advisor; Karen Nelson, Democratic Deputy Committee Staff Director, Health; Anne Morris Reid, Democratic Senior Professional Staff Member; and Rachel Sher, Democratic Senior Counsel.

Mr. PITTS. The subcommittee will come to order. The Chair will recognize himself for an opening statement.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Today's hearing relates to the 21st Century Cures Initiative announced by the Energy and Commerce Committee on April 30, 2014. This Cures effort is envisioned to explore ways to accelerate

the discovery, development and delivery cycle for new medical breakthroughs. Through this effort, Congress hopes to clear a path to find more cures and treatments, while also creating jobs, and keeping America as the innovation center of the world.

Shortly following the announcement of the Cures Initiative, the committee issued a white paper on May 1, 2014, entitled 21st Century Cures: Call for Action, which more fully discusses the ideas behind the Cures project and issues of call to action, call for ideas. The first goal of this project is to solicit ideas. Congress does not have all the answers, but we do have a role to play in ensuring our Nation's laws and regulations, keep pace and compliment the biomedical research and innovation that is happening at lightning speed.

Earlier this month, we heard from the NIH, FDA, patient advocates, university leaders, and other scientific pioneers about their ideas, challenges and successes. Today, we will hear from experts who contributed to the President's Council of Advisor on Science and Technology, PCAST, report on propelling innovation in drug discovery, development and evaluation. This important report hits on a number of topics that we will have to explore if we are to truly advance Cures. These ideas include, among others, making sure incentives are in place to ensure capital is flowing towards research and development of new cures, and designing clinical trials to the appropriate size and scale, given the growth of targeted personalized medicine.

Today, we hope to learn more about these proposals and others put forth by PCAST, and determine which ideas or recommendations could potentially advance the 21st Century Cures Initiative.

Excitingly, the fight for faster cures in the 21st century will not only foster medical innovations, but it can also make our healthcare system more efficient, and can save lives.

I want to welcome our witnesses today. I look forward to learning more about the advancements in biomedical research and innovation.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

Today's hearing relates to the 21st Century Cures Initiative announced by the Energy and Commerce Committee on April 30, 2014. This Cures effort is envisioned to explore ways to accelerate the discovery, development, and delivery cycle for new medical breakthroughs. Through this effort, Congress hopes to clear a path to find more cures and treatments while also creating jobs and keeping America as the innovation center of the world.

Shortly following the announcement of the Cures initiative, the committee issued a white paper on May 1, 2014 entitled "21st Century Cures: A Call to Action" which more fully discusses the ideas behind the Cures project and issues a call to action—a call for ideas.

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centives are in place to ensure capital is flowing toward research and development of new cures and designing clinical trials to the appropriate size and scale given the growth of targeted, personalized medicine.

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I want to welcome our witnesses today and look forward to learning more about the advancements in biomedical research and innovation.

Mr. PITTS. And I ask for unanimous consent to include the following statements for today's hearing record from Dr. Raymond Woosley, former president of the Critical Path Institute and one of the experts that participated in the development of the PCAST report, and Dr. Janet Woodcock, Director of FDA Center for Drug Evaluation Research Blog Post, "Progress on the 2012 Drug Innovation report by PCAST" from May 20, 2014.

Without objection, so ordered.

[The information follows:]

Written statement to the

U.S. Congressional Committee on Energy and Commerce

Subcommittee on Health

Hearing on "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation"

May 20, 2014

Raymond L. Woosley, MD, PhD
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Members of the Committee:

I am Dr. Raymond Woosley, President of AZCERT, a non-profit organization created to foster the safe use of medicines. I have over 35 years of experience in academia, the pharmaceutical industry and in the non-profit sector. The greater part of my career in clinical pharmacology and cardiology has been spent creating inter-professional and inter-disciplinary programs to improve medical outcomes with medications. I have led federally funded programs in clinical research such as the General Clinical Research Center at Georgetown (now termed CTSA's) and an AHRQ funded Center for Education and Research on Therapeutics (CERTs) in Arizona. I was formerly Vice-President and Dean of the College of Medicine at the University of Arizona and in 2005 I left to found the Critical Path Institute (C-Path), a partnership between the FDA, the biopharmaceutical industry and academic scientists dedicated to developing consensus on best practice methods in drug development. These experiences have convinced me that partnerships and inter-disciplinary approaches are not only effective, they must be at the core of our national plan for biomedical innovation.

Like many previous reports, the 2012 PCAST report summarizes the serious problem that was first recognized almost a decade ago when FDA Commissioner Dr. Mark McClellan called attention to the declining number of innovative new medical products being submitted to the FDA, in spite of a 250% increase in the nation's research and development (R&D) investment. Today, the United States invests over $30 billion each year in NIH-funded research, more than the rest of the world combined, yet, only 30-40 innovative new medications reach the market each year. In fact, the number is essentially unchanged since 1975. Doubling of the NIH budget and increasing investments in pharmaceutical R&D have not changed the number of truly innovative new drugs that reach patients each year.

The PCAST report set as a national goal the doubling of the number of innovative new biomedical products that reach the market over the next 10-15 years. Considering the combined $100 Billion spent annually for biomedical R&D by industry and the federal government, this seems to be a terribly modest target, one that is not substantially different from the status quo. However, we cannot even assume that the status quo will not become worse. Figure one in the PCAST report shows that since 2008, pharmaceutical investments in R&D are in decline. The status quo, however unpleasant, may not continue if biopharmaceutical investment continues to decline and other changes are not made.

The first recommendation in the report calls for continued support of basic biomedical research, NCATs and the Reagan-Udall Foundation (RUF). In addition to NCATS and RUF, there are many other important federal programs that now have minimal funding and are just as important for completing the innovation "supply chain" as discussed below. The PCAST report calls for creating yet another under-funded super-committee, a broad based Partnership to Accelerate Therapeutics (PAT). The report likens the PAT to the Institute of Medicine's Drug Forum but anticipates that it will be more

successful. Experience with this, and previous under-funded, broadly represented discussion forums, would argue that the PAT will not have substantive impact.

The PCAST report failed to propose any bold initiatives that could have meaningful impact on the mammoth problem at hand or that could even reach the report's modest target of doubling the current low level of productivity of the biomedical research enterprise. It discusses, but discounts, the only bold alternative that was raised by the PCAST consultants, i.e. a SEMATECH for biopharmaceutical development. Perhaps it could be named "BIOTECH". Bold initiatives are often suppressed because funding is unlikely or they threaten powerful stakeholders who are inextricably wed to the current paradigm. The question is not whether a SEMATECH-like organization is needed but... What would it do? SEMATECH was not a convener nor was it simply a forum for discussion of the problem. It brought scientists from government, industry and academia together to identify the reasons why US-made computer chips were failing and it employed applied science solutions such as establishing manufacturing standards and defining best practices. It did not compete with the established organizations working in the field. It brought them into the improvement process and utilized their unique skills and expertise.

An empowered and inclusive BIOTECH could restructure the nation's current investment which is grossly imbalanced toward discovery science ($30 billion) on one end and market approval (over $46 billion) on the other. As shown below, nine other essential links in the supply chain share less than $600 million in support. The following are my rough estimates of current funding across the innovation supply chain (Color added for emphasis of funding gap):

- Discovery: $30 billion (NIH)

- Replication/Validation of discovery: $ 40 million by the Accelerated Medical Partnership (AMP)
- Translational research on mechanism of disease: $ 485 million at NCATS & Cures Action Network
- Biomarker discovery: $ 30 million by TransCelerate Biopharma and FNIH's biomarker consortium
- Biomarker qualification & best practices in R&D: $ 5 million for Critical Path Public Private Partnerships by FDA
- Regulatory Science: < $ 5 million by FDA, NIH and RUF
- Data Standards for clinical research: < $5 million by CDISC
- Biological Standards for biomarker assays: < $5 million by NIST
- Training of Clinical Investigators: < $20 million by NIH
- Methods for post-market surveillance: < $10 million by AHRQ and FDA (mini-Sentinel)

- Development: $45 Billion by biopharma industry
- Review and approve new products: $1.2 billion for FDA review(includes user fees)

Each of these roles is an essential element in an efficient and productive supply chain for discovery, development and marketing of innovative new products. Any under-resourced element in the chain is its weakest link, and there are several.

I believe that the funding gap between discovery and development shown above is a major contributor to the "valley of death" for new products.

What could a balanced, inter-linked ecosystem do to support development of scientific discoveries and enable new product development?

1. Create confidence in the discovery – make validation of biomarkers and drug targets as the first critical step in the discovery process (a discovery that cannot be replicated is not a discovery but an expensive distraction)
2. Understand diseases at the molecular level – research networks that study and understand the mechanism of disease
3. Know exactly who has the disease of interest - Registries that define and identify the sub-populations appropriate for testing with new candidate therapies.
4. Identify biomarkers of drug action that are founded on solid, cutting edge science and measured using reproducible, standardized methods.
5. Identify methods of drug testing and development that are "best of breed" and accepted by a consensus that includes multiple developers and regulatory agencies.
6. Establish common data elements for clinical research that bring greater efficiency to analysis of data from multiple sources and enable modeling and simulation of development strategies.
7. Create tools and infrastructure in medical practice that enable rapid learning in order to determine whether innovations are safe, have efficacy and are cost effective.

What can BIOTECH deliver: A balanced, synchronous approach to development

Bringing balance and synchrony to the supply chain continuum will require either new or redirected federal funding. Synchrony will require a forum for open dialog, scientific interchange and the authority to set priorities, to define technical standards and to identify best practices in development. SEMATECH provided the semiconductor industry with that forum and the required synchrony. For SEMATECH, Congress and the semiconductor industry shared the burden of funding. Congress and the biopharmaceutical industry should unite to bring all stakeholders working in the supply chain under the umbrella of BIOTECH.

If given the authority and the resources, BIOTECH could play an essential role by assuring that each element in the chain is seamlessly connected and has the necessary funding to produce the applied science and the development tools that are needed by developers.

Candidate organizations and their potential roles within BIOTECH could include:

- FNIH – raise funds to perform specific projects of interest to BIOTECH and the NIH, especially NCATS
- Reagan-Udall Foundation – raise funds to perform specific projects of interest to BIOTECH and FDA
- CDISC – Establish data standards for clinical research and disease data elements
- NIST – Establish performance standards for laboratory methods to assay biomarkers
- C-Path – Establish consensus between regulators and developers for best practices in testing and evaluation of new drugs
- NCATS (CTSAs) – Establish clinical research networks and registries for specific illnesses
- CDC drug surveillance program – Establish post-market drug/biologic/device surveillance (Sentinel system)

A balanced supply chain approach will require a focus on better funding for applied science, modernization of the research infrastructure, technology standards and verification of scientific validity at all stages of the innovation supply chain. It will require investment in healthcare practice environments in order to make it a truly learning healthcare environment for rapid testing and development of new medical products. The use of clinical trial networks and patient registries, already of proven value, should be made integral components of medical practice. Innovative approaches to rapid and efficient learning from research such as Vanderbilt Medical Center's clinical research program should be the norm for the nation. Such changes require a bold vision such as a SEMATECH for biopharmaceuticals. i.e. BIOTECH.

Thank you for the opportunity to present this recommendation to the Committee.

Raymond L. Woosley, MD, PhD
President, AZCERT

Progress on the 2012 Drug Innovation Report by PCAST (President's Council of Advisors on Science and Technology)

Posted on **May 20, 2014** by **FDA Voice**

By: Janet Woodcock, M.D.

More than 18 months ago, a group of Presidential advisors from industry, academia and the Federal government concluded that while the basic biomedical sciences have seen stunning progress in past decades, challenges remain in translating those scientific advances into practical solutions. To accelerate the development of new therapies, the President's Council of Advisors on Science and Technology (PCAST) made a number of recommendations that called for action by all of the players in the innovation ecosystem including industry, academia, health care professionals and such federal agencies as the National Institutes of Health, the Centers for Medicare and Medicaid Services and the FDA.

PCAST's detailed list of recommendations for FDA generally fell into four categories: advancing regulatory science through public private partnerships; encouraging the expedited approval of drugs; improving FDA's tools for monitoring and communicating clinical benefits and risks and reforming the agency's management practices. A review of all four categories suggests that, together, FDA, Congress, industry and patient groups have made significant progress towards addressing

these recommendations since the PCAST report was released in September 2012, although some critical challenges remain.

Public-private partnerships: Just like PCAST, FDA believes that bridging the gap between drug discovery and development can only be achieved through creative collaborations. Public-private partnerships enable stakeholders to leverage expertise and resources for the conduct of mutually beneficial research activities in the precompetitive domain. And indeed, our Center for Drugs is involved in 22 science-driven, public-private partnerships that promote development of research tools, platforms, clinical databases and predictive models to advance knowledge of disease and safety profiles of drugs – some of which were funded under legislation authorized in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). The recent approval of Zykadia, for patients with a certain type of late-stage (metastatic) non-small cell lung cancer, benefited from FDA's collaborative efforts with industry, health advocacy organizations and others to identify the molecular underpinnings of cancer that would make it possible to classify and treat cancer by specific subtype.

Expedited review: Even before the PCAST report was issued, FDA had a number of expedited development and review programs in place. Accelerated approval allows for approval of drugs for serious conditions that fill an unmet need based on the drug's effect on a surrogate endpoint that is thought to predict clinical benefit. This can speed access to a potentially important new drug, where it might take years of study to demonstrate a survival benefit or other longer-term outcome. Fast track allows sponsors with drugs that qualify to have more frequent meetings and communications with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval. Priority review shortens the review time for certain promising drugs from 10 months to six months.

Nearly half of the 27 novel drugs approved by FDA last year took advantage of these expedited pathways, which were expanded and enhanced with the help of Congress under FDASIA. Also of note, these novel drugs were approved in as little time as 4.5 months, without compromising our high standards for safety and efficacy.

In a demonstration of the significant progress that can be made when all stakeholders come together, Congress, FDA, industry and patient groups joined together to create the Breakthrough Therapy Designation in FDASIA. This new pathway is designed for those drugs intended to treat serious or life-threatening diseases or conditions where there is preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint or set of endpoints. A drug that receives Breakthrough Therapy designation is eligible for all Fast Track designation features; intensive guidance on an efficient drug development program, beginning as early as Phase 1; and the commitment from FDA's review staff, including senior managers, to work closely together throughout the drug development and review process. To explain the concepts underlying these expedited programs and help companies decide whether these expedited review

programs will fit their drug, we issued a draft guidance document last June and will be issuing a final guidance soon. So far we have received 178 breakthrough designation submissions, granted 44 designations, and already approved six of the designated drugs, four of which were new molecular entities and two were for new indications for already approved drugs.

PCAST also recommended that FDA implement a drug approval pathway under which sponsors could propose, early in the development process, to study a new drug for initial approval that would be reserved for use in a specific subgroup of patients, this would thus allow a narrower development program than required for traditional approvals. While FDA has existing authority to approve products for subpopulations, in practice, drug development protocols generally evaluate risks in a broader population, resulting in larger, lengthier trials. FDA agrees that a more clearly defined Special Medical Use or Limited Population pathway could encourage novel limited population development protocols and complement FDA's existing efforts to get drugs to small populations in need faster. Legislation focused on a pathway for drugs for serious or life-threatening bacterial infections in patients with unmet medical need – a particular area of unmet medical need highlighted in the PCAST report – has been introduced to address this issue and we welcome the opportunity for continued discussions with stakeholders.

Communicating risks and benefits: To help guide our review process for both standard and priority review drugs, we are implementing a structured Benefit-Risk Assessment framework, as agreed to as part of our successful negotiation with industry on user fees to fund drug review activities. Information on the current statement of knowledge regarding the condition and the available therapies, the drug's individual benefits and risks and their frequency, and any efforts that could mitigate the safety concerns are put together in a table. We are currently seeking to integrate this framework into our existing review templates and memos. The purpose is to ensure better communication of the review teams thinking during review and, most importantly, FDA's decision-making when the agency approves a product.

Management reforms: PCAST urged a variety of management reforms, some involving staff and some involving infrastructure. We are actively modernizing our information technology platforms to advance innovation and prepare for the enormous data sets that drug sponsors are submitting from clinical studies using genome sequencing and as part of the user fee agreements we are piloting a process change that improves communication during the review process.

Much progress has been made on the PCAST recommendations through FDASIA, user fee agreements, collaborative efforts with stakeholders and the agency's own efforts to continue to improve. And yet, we recognize that challenges remain to advance policies that enhance biomedical innovation and encourage the translation of exciting discoveries into effective therapies. FDA intends to continue working on the PCAST recommendations along with our other partners in the innovation ecosystem.

Janet Woodcock, M.D., is the Director of FDA's Center for Drug Evaluation and Research

This entry was posted in **Drugs** and tagged **2012 Drug Innovation Report**, **President's Council of Advisors on Science and Technology (PCAST)** by **FDA Voice**. Bookmark the **permalink [http://blogs.fda.gov/fdavoice/index.php/2014/05/progress-on-the-2012-drug-innovation-report-by-pcast-presidents-council-of-advisors-on-science-and-technology/]** .

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Mr. PITTS. Thank you. I yield the remainder of my time to Dr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman. Thank you for yielding. Thank you for having this hearing, and especially thanks to the chairman and ranking member of the full committee for pursuing the 21st Century Cures Agenda.

So this is an accompanying bipartisan effort to listen to you, the scientists, to listen to doctors, listen to researchers, listen to patients, and, yes, we will listen to government agencies to find out how we can continue to lead the world in scientific discovery that ultimately leads to cures, treatments, medical devices that will improve human health, and, most importantly, alleviate human suffering.

In September 2012, the President's Council of Advisors on Science and Technology issued a report to the President on propelling innovation in drug discovery, development and evaluation. The report provided recommendations on how to ensure we are doing everything we can to capture the significant amount of knowledge that has been gained in the last few decades, and to ensure that the knowledge is translated into cures and actually make it into the lives of patients. The report found many of the same themes that we have heard for the last 10 years in this committee. While our scientific knowledge has significantly grown, the promise of that knowledge has not been realized. The recommendations of the President's council also mirror familiar suggestions, including building off existing authorities to accelerate therapeutics and ensure management of regulatory agencies appropriately balances the benefits and risk. With this—when this effort was launched, we said we wanted to hear from everyone, and I am pleased that we are evaluating the advice that is being given to the President in this area.

I certainly look forward to this hearing. I look forward to your testimony. I look forward to all of the participation of our witnesses.

Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the ranking member, Mr. Pallone, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts, and thank you for calling this hearing.

I wanted to initially ask unanimous consent to enter into the record a—an article on the progress of the 2012 Drug Innovation report by PCAST, if I could. I believe you have it, Mr. Chairman.

Mr. PITTS. Yes, we just did that.

Mr. PALLONE. All right, thank you.

Let me also thank Chairman Upton for convening the 21st Century Cures Initiative, and also Ms. DeGette, who was very much involved with that.

We all agree that the Federal Government and Congress can play a role to help accelerate the discovery, development and delivery of promising new treatments to patients, and the question remains how to best advance those goals. I look forward to engaging this process as we meet with stakeholders, and gather ideas and input from experts on what, if any, policies Congress can consider moving forward. And most importantly, I look forward to working with my colleagues in a bipartisan way to ensure that promising new medicines get to patients in a timely manner, and they are safe and effective.

The committee already has a great record on that effort, most recently with the passage of the FDA Safety and Innovation Act of 2012, or FDASIA. That law reformed and revitalized many FDA programs to improve its regulatory scheme, to facilitate a more efficient and predictable review process. Specifically, we updated the regulatory pathways under which FDA provides for expedited reviews of drugs. WE also aided for the first time the breakthrough therapy, Pathway, and all of these programs served a goal of helping drug sponsors and the FDA work together to cut development time.

In addition, I am currently working with Chairman Pitts on a Bill that would streamline the DEA's scheduling process as it relates to improved drug therapies. If we are going to have a comprehensive discussion about how to promote innovation and medical advancements, we can't simply focus on the FDA. The work being done at NIH and through the country at research universities like my hometown school of Rutgers University, has to be properly funded. Discovering cures and developing effective treatments are complex, difficult and expensive endeavors. NIH is the premiere biomedical research institution in the world, and I hope this committee can find ways to ensure that NEH—NIH has the necessary tools to maintain that designation.

When we talk about the delivery of therapies, we have got to address access. Medical advances and cures at the earliest possible time is our shared goal, but we all must work together to ensure that when discovered, those cures can get to all patients, and not just those who can afford them.

So, Mr. Chairman, based on your comments and actions to date, I am hopeful we will have these conversations as we move forward. Today, the committee will examine the President's Council of Advisor on Science and Technology, or PCAST, Report on Drug Innovation. That report issued in September of 2012, only a couple of months following the passage of FDASIA, puts forth a number of proposals across a large spectrum of policies, from funding basic biomedical research, to developing economic initiatives. And there are a number of ideas in this report, so I look forward to flushing out their relevance, and thank everyone for their input today in moving forward.

And I have about a minute and a half. I would like to yield to my colleague from Texas, Mr. Green.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you to our ranking member and the Chair for having this hearing, and our witnesses for testifying, and yielding the time.

I applaud the committee for its 21st Century Cures Initiative to examine what steps are needed to harness scientific knowledge, and accelerate the pace of the new Cures. The—in 2012, this committee took an important first step in addressing the lack of new drug development to treat drug-resistant infections. Our committee colleague, Congressman Gingrey, and I were the lead sponsors of that legislation, along with a number of our other colleagues on the committee, but I fear our work is far from finished. According to the report recently by the WHO last month, the antibiotic crisis is bigger and more urgent than the AIDS epidemic of the 1980s, and without swift and significant action, the implications will be devastating. The GAIN Act was an important step to address—addressing a lack of new drug development, but it must not be the last. Weekly reports of new global threats and cases identified here at home are a stark reminder our ability to meet this threat relies in no small part upon a robust pipeline and new therapies. PCAST, scientists, physicians and global health leaders have sounded the alarm. We need new incentives and approaches to continue fighting drug-resistant bacteria and build on the work of getting it started. It would be wrong to let this opportunity for action pass us by.

I urge the committee to address this crisis head-on, and encourage meaningful development in the antibiotic space. I stand ready to work with you to achieve this worthy goal, and we do not have a moment to waste.

And I yield back my time. Thank you.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the chairman of the full committee, Mr. Upton, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Well, thank you, Mr. Chairman.

So today marks our first 21st Century Cures hearing at the Health Subcommittee. We launched this bipartisan initiative earlier this month with one primary goal: accelerate the pace of the discovery, development and delivery cycle so that we can get innovative new cures and treatments to patients more quickly.

Today, we continue this important conversation with several of the distinguished experts who contributed to the President's Council of Advisors on Science and Tech Report on Drug Innovation. The President, in soliciting recommendations on this very important topic, decided propelling drug innovation is a policy worthy of exploring and advancing, and I couldn't agree more.

In their report, the President's advisors found that the Nation's biomedical innovation ecosystem is under significant stress, citing the patient—citing the patent cliff facing the pharmaceutical industry, declining investment from venture capital, and decreasing research and development in critical area, including Alzheimer's. We

have heard similar concern in our discussion with patients, innovators and thought leaders.

So in order to address these issues facing our biomedical innovation ecosystem, the experts who contributed to the report recommended closing scientific knowledge gaps, addressing inefficiencies in clinical trials, considering more economic initiatives to decrease investment—to increase investment, and encouraging even more innovation at the FDA. The President's advisors put forth the following goal for our Nation. "Double the current annual output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry academia and Government working together to double the efficiency of drug development by decreasing clinical failure, clinical trial cost, time to market, and regulatory uncertainty." I know that we can all agree to join the President and his advisors to meet that goal.

As the President's advisors so rightly said, we must work together to achieve the goal. This has to be a collaborative effort.

The committee recently put out a call for feedback on the PCAST report. We also asked for input from our Nation's patients on the discovery of treatment and cures for their diseases. The 21st Century Cures Initiative ultimately touches everybody, every family, patients, doctors, loved ones, researchers, thought leaders, everyone, and we want input from all of those involved. Folks can email their ideas to Cures@mail.house.gov, and contribute to the conversation on Twitter and Facebook using hashtag #Pathtocures. Together, I know that we can provide hope to patients and families across our great country, and keep America at the forefront of innovation, and, by the way, create lots more jobs too.

Mr. Chairman, I yield back my balance of my time.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Today marks our first 21st Century Cures hearing at the Health Subcommittee. We launched this bipartisan initiative earlier this month with one primary goal: accelerate the pace of the discovery, development, and delivery cycle so we can get innovative new cures and treatments to patients more quickly. Today, we continue this important conversation with several of the distinguished experts who contributed to the President's Council of Advisors on Science and Technology report on drug innovation.

The President, in soliciting recommendations on this important topic, decided propelling drug innovation is a policy worthy of exploring and advancing. I could not agree more.

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In order to address these issues facing our biomedical innovation ecosystem, the experts who contributed to the report recommended closing scientific knowledge gaps, addressing inefficiencies in clinical trials, considering new economic incentives to increase investment, and encouraging even more innovation at the Food and Drug Administration.

The President's advisors put forth the following goal for our Nation:

"Double the current annual output of innovative new medicines forpatients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia, and Government working together to double the efficiency of drug development, by decreasing clinical failure, clinical trial costs, time to market, and regulatory uncertainty."

I think we can all agree to join the President and his advisors in meeting this goal.

As the President's advisors so rightly said, we must work together to achieve this goal. This must be a collaborative effort. The committee recently put out a call for feedback on the PCAST report. We also asked for input from our Nation's patients on the discovery of treatments and cures for their diseases. The 21st Century Cures Initiative ultimately touches everyone—patients, doctors, loved ones, researchers, thought leaders—and we want input from all those involved. Email your ideas to cures@mail.house.gov and contribute to the conversation on Twitter and Facebook using the hashtag #Path2Cures. Together we can provide hope to patients and families all across the country and keep America at the forefront of innovation.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman.

Today, we continue our work on the 21st Century Cures Initiative. These hearings are important. We need to ensure that patients gain access to new treatment and cures at the earliest possible time. At the same time, we need to recognize the strengths of our current system which has led to enormous breakthroughs in drugs and devices. FDA reviews and approves drugs faster than any other regulatory agency in the world. NIH and FDA are world leaders in clinical trial design, and in integrating the newest science into their policies and approaches, and our system protects the health of patients.

It is critical that we avoid any attempt to fix things that aren't broken, and, in the process, do harm to a system that is already working very well. We should create policies that foster scientific advances, but we should do so in a way that does not jeopardize public health.

Across the board, when we have an informal meeting, participants at the roundtable 2 weeks ago said that we need to assure that NIH has the resources necessary to maintain its national and international leadership in biomedical research, and I would welcome an opportunity to work with Chairman Upton, and all of our colleagues on both sides of the aisle, on accomplishing that goal.

The participants at that roundtable also indicated that FDA was generally excelling in drug and device oversight, and I was glad to hear that investment in the life sciences was booming. Mr. Left, one of the people there, attributed that success, at least in part, to some of the reforms we put into place in the 2012 FDA Safety and Innovation Act.

The PCAST report makes several recommendations relating to FDA. There are two I would particularly like to learn more about. One is the recommendation that FDA or Congress develop new voluntary pathway to facilitate the approval of drugs for special medical uses based on smaller clinical trials that would be needed for broader uses. A bipartisan Bill is introduced that would create such a pathway for antibiotics for serious or life-threatening infections for which there are few, if any other, options. This is an area of increasingly dire need, and I think this Bill warrants serious con-

sideration. As written, however, it does not achieve what PCAST described as an essential component of the pathway that the drug's labeling send a clear and effective signal that it should be reserved for use in the specific subgroup of patients for which it was approved. I would be interested in our witnesses telling us their views on this issue.

The other recommendation is the FDA undertake pilot projects to explore certain kinds of provisional approval pathways. These so-called adaptive approval pathways shift more of the data requirements to post-market studies, however, PCAST recommended that Congress not legislate in this area yet because serious questions still need to be addressed. These include appropriate evidentiary standards, protection of patients, and the ability to ensure that drugs are withdrawn if their effectiveness is not subsequently demonstrated. I would like to hear more about that.

I was disappointed that FDA and NIH were not invited to participate in today's hearing. I appreciate it, Mr. Chairman, that you entered the FDA blog into the record. It shows the significant progress FDA has made in meeting the recommendations of the PCAST report.

And I would like to now yield the balance of my time to our colleague, Ms. DeGette, from the State of Colorado.

OPENING STATEMENT OF HON. DIANE DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. DEGETTE. Thank you very much, Mr. Waxman. And thanks, Mr. Chairman, for holding this hearing on the President's Council of Advisors on Science and Technology Report on Drug Innovation.

As has been mentioned, I joined with Chairman Upton to launch the 21st Century Cures Initiative about a month ago. We had a very successful kickoff roundtable with other members of this committee, where we heard from a number of experts, top leaders from the administration, academia, research and industry, to dig deep into how we can effectively and efficiently tackle some of the more complex challenges in medicine.

As the next step in this endeavor, it was important to consider what types of recommendations relating to research and innovation have already been proposed. The report that we will discuss today, as has been mentioned, provides 8 recommendations, ranging from Federal funding for basic biomedical research, to improved drug evaluation. The report also highlighted what can happen when lawmakers work together on a bipartisan basis to pass legislation that addresses emerging medical needs.

There are several Bills that I support, which have been mentioned both by the witnesses in their testimony, as well as the other Members today. A couple of them that have not been mentioned are the Antibiotic Development to Advance Patient Treatment, or ADAPT Act, and the Regenerative Medicine Promotion Act of 2014, of which I am the prime sponsor.

So there is a lot going on. I think the testimony today will be a good step along our path to figure out how we can work together toward improving research and innovation.

Thank you very much, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentlelady.

That concludes the opening statements, but opening statement of all the other Members will be made a part of the record.

We have one panel with us today, five witnesses, and I will introduce them in the order that they speak.

Dr. Garry Neil, Global Head of Research and Development for Medgenics; Ms. Sara Radcliffe, Executive Vice President, Biotechnology Industry Organiation; Mr. Frank Sasinowski, Director, Hyman, Phelps and McNamara; Mr. Jeff Allen, Executive Director, Friends of Cancer Research; Dr. Sean Tunis, Found and CEO, Center for Medical Technology Policy.

Thank you for coming. Your written testimony will be made a part of the record. You will be each given 5 minutes to summarize your testimony.

And, Dr. Neil, we will start with you. You are recognized for 5 minutes for your opening statement. Push the button, yes.

STATEMENTS OF GARRY A. NEIL, GLOBAL HEAD OF RESEARCH AND DEVELOPMENT, MEDGENICS, INC.; SARA RADCLIFFE, EXECUTIVE VICE PRESIDENT FOR HEALTH, BIOTECHNOLOGY INDUSTRY ORGANIZATION; FRANK J. SASINOWSKI, DIRECTOR, HYMAN, PHELPS & MCNAMARA, P.C., ON BEHALF OF NATIONAL ORGANIZATION FOR RARE DISORDERS; JEFF ALLEN, EXECUTIVE DIRECTOR, FRIENDS OF CANCER RESEARCH; AND SEAN R. TUNIS, PRESIDENT AND CHIEF EXECUTIVE OFFICER, CENTER FOR MEDICAL TECHNOLOGY POLICY

STATEMENT OF GARRY A. NEIL

Mr. NEIL. Sorry. Chairman Pitts, Ranking Member Pallone, Ranking Member Waxman, and Members of the committee, thank you for the opportunity to testify before you this morning.

My name is Garry Neil and I head research and development in Medgenics, a small biotechnology company in Wayne, Pennsylvania, with operations in the U.S. and in Israel. My colleagues and I are working to bring novel ex vivo gene therapies to patients with serious, rare and orphan diseases. I am a physician, and have spent the past 30 years in biomedical research and academia in industry, where I have worked in both large and small companies. I have also spent time in venture capital, and I have been engaged with a number of nonprofit organizations in support of the missions of FDA, NIH, and industrial research and development, and these include the Foundation for the NIH, the Reagan-Udall Foundation for the FDA, the Biomarkers Consortium, and TranCelerate Biomedical, an industry collaboration I helped found in 2012. I provided expert input into the 2012 PCAST report, and I am here today representing myself.

The American Biomedical Research and Development Ecosystem remains the envy of the world. Its value is immense, and I am sure that all of us in this room have benefitted from medical innovation driven by that system in some way or other. Biomedical innovation employs nearly 1 million people in the U.S., and exports from the biopharmaceutical industry reached nearly $47 billion in 2010, but

beyond the economic impact, it provides increasingly effective treatments and hope for patients everywhere.

The PCAST report identified a series of challenges and obstacles that continue to raise cost, lengthen timelines, and increase risk, including difficulties in translating basic scientific discoveries into therapies, inefficiency of clinical trials, and the need to streamline the regulatory process, as well as the need to ensure that appropriate incentives are in place to encourage investment in U.S. biomedical research. But since the release of that report, a number of important developments have occurred demonstrating the resilience of the system. The FDA Safety and Innovation Act of 2012 expanded the use of accelerated approval, and introduced a new breakthrough designation, both very helpful. TranCelerate Biomedical, as I mentioned, was launched as an industry collaboration to improve the efficiency of clinical trials. It currently has 16 member companies, and has embarked on a number of projects aimed at reducing operational bottlenecks faced by all sponsors. Early results are extremely encouraging. The accelerating medicines partnership, a public-private partnership between NIH, the pharmaceutical industry and patient advocacy groups, was established and will address Alzheimer's Disease, diabetes and others.

At the Reagan-Udall Foundation, a public-private partnership created by Congress to support regulatory science, post-marketing safety surveillance is being advanced by the Innovation in Medical Evidence Development and Surveillance Project. And as Mr. Waxman noted, venture capital investment of biomedical research has started to increase again. Biotechnology investment dollars rose 8 percent in 2013 to $4.5 billion. These are encouraging signs, but much more needs to be done if we are going to reach the ambitious goals set in the PCAST report, and maintain our global leadership and life sciences, as well as address the healthcare challenges that confront the country now.

Additional help and leadership from Congress on this would be tremendously beneficial, and areas for Congress to target include facilitating the creation of clinical trial networks, investing in new biomarkers and clinical trial endpoints, increasing and sustaining funding for both FDA and NIH, expansion of public-private partnerships to support the scientific missions of both FDA and NIH, providing FDA with increased flexibility to accelerate programs for lifesaving medicines, and examining existing incentives for capital investment of biomedical research.

Our company, like hundreds of other small innovative companies, faces many of these challenges every day. Our scientists, like virtually all industry scientists, are incredibly dedicated, driven and focused. Their ingenuity and problem-solving amazes me every day, and we are making rapid progress. We rely heavily upon collaboration with academic scientists who advise us, and also upon the regulators who help us to find the path forward. We also rely upon our investors. They risk their capital because they believe we will succeed. Clearly, there is no time or resource to spare. We lay every decision, every experiment with the utmost care. We understand the implications for our people, our investors, the country, but most importantly for the patients and their parents who are desperately waiting for cures.

I applaud the committee for undertaking this effort, and the sincere belief that it can result in positive change. Enlightened, science-driven policy will allow companies like Medgenics to succeed, put the next generation of transformational therapies in the hands of caregivers around the world, and increase the competitiveness and prosperity of our country. Thank you.

[The prepared statement of Mr. Neil follows:]

Executive Summary

Testimony Before the Committee on Energy and Commerce

Health Subcommittee Hearing

21st Century Cures: The PCAST Report on Drug Innovation

Garry A. Neil, MD

May 20, 2014

The American biomedical research and development ecosystem remains the envy of the world. It's value to the US and the world is immense with respect to jobs, export and new therapies. It is imperative that we continue to invest to maintain our global lead in biomedical research.

The 2012 PCAST report, "Propelling Innovation in Drug Discovery, Development and Evaluation" identified a series of challenges and obstacles that raise costs, lengthen timelines and increase risk. These include difficulties in "translating" basic scientific discoveries into developable therapies, inefficient clinical trials, the need to streamline the regulatory process and the need to ensure that appropriate incentives are in place to encourage investment in US biomedical research.

Since its release there are encouraging signs of improvement but much more needs to be done if we are going to reach the ambitious goals set in PCAST report.

Areas for Congress to target are:

- Facilitation the creation of clinical trial networks
- Investment in new biomarkers and clinical trials endpoints
- Increasing and sustaining funding for both FDA and NIH including new programs to expand scientific expertise in translation and clinical trials and staff development
- Expansion of Public Private Partnerships to support the scientific mission of both FDA and NIH
- Ensuring FDA has the increased flexibility to accelerate development programs for life saving medicines
- Examination of existing incentives for capital investment

Testimony Before the Committee on Energy and Commerce

Health Subcommittee Hearing

21st Century Cures: The PCAST Report on Drug Innovation

Garry A. Neil, MD

May 20, 2014

Chairman Pitts, Ranking Member Pallone and members of the Committee thank you for the opportunity to testify before you this morning. My name is Garry Neil. I am privileged to head Research and Development in Medgenics, a small biotechnology company headquartered in Wayne, Pennsylvania with operations in the US and in Israel. My colleagues and I are working to bring novel ex-vivo gene therapies to patients with serious rare and orphan diseases. I am a physician and have spent the past 30 years in biomedical research in academia and industry, where I have worked in both large and small companies. I have also spent time in venture capital. I have also been engaged with a number of non-profit organizations in support of the missions of FDA, NIH and industrial R&D. These include membership on the Boards of Directors of the Foundation for the NIH, the Reagan-Udall Foundation for the FDA, the Science Management Review Board of the NIH, the Biomarkers Consortium and Transcelerate Biomedical, an industry collaboration I helped found in 2012 to address inefficiencies in industry sponsored clinical trials. I also provided expert input into the 2012 PCAST report, "Propelling Innovation in Drug Discovery, Development and Evaluation."

I am here today representing myself.

The American biomedical research and development ecosystem remains the envy of the world. Its value to the US and the world is immense. Biomedical innovation employs nearly one million people and exports from the biopharmaceutical industry reached nearly $47 billion in 2010[1]. Beyond economic impact it provides increasingly effective treatments and hope for patients everywhere.

The PCAST report comprehensively documented the state of the biomedical research and development "ecosystem" and identified a series of challenges and obstacles that raise costs, lengthen timelines and increase risk including the difficulties in "translating" basic scientific discoveries into developable therapies, inefficient clinical trials, the need to streamline the regulatory process and the need to ensure that appropriate incentives are in place to encourage investment in US biomedical research[1].

Since the release of the report a number of important developments have occurred demonstrating the resilience of the ecosystem.

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 expanded the use of accelerated approval and introduced a new "breakthrough" designation[2]. As of April 2014 the agency had received 178 requests for breakthrough designation[3]. Forty-four have been granted, and six drugs have been

approved for use under this pathway[3]. Under Commissioner Hamburg's leadership the FDA has continued to be the world's leading regulatory agency with 74% of new drugs globally being approved first in the USA[4]. Many of the 37 new drugs and biologics approved in 2012 and 27 in 2013 are first in class, targeted medications[4].

Transcelerate Biomedical was launched as an industry collaboration to improve the efficiency of clinical trials[5]. It currently has 16 member companies and has embarked on a number of projects aimed at reducing operational bottlenecks faced by all sponsors. Early results are extremely encouraging[6].
The National Center for Advancing Translational Sciences (NCATS) of the NIH has now been operationalized[7].

The Accelerating Medicines partnership, a public private partnership between NIH, the pharmaceutical industry and patient advocacy groups was established and will address a number of important diseases including Alzheimer's disease, diabetes, rheumatoid arthritis and lupus[8].

Another public private partnership, the lung cancer master protocol, a molecular biomarker-driven, multi-drug, phase 2/3 registration trial in lung cancer has been activated. The participants include The Friends of Cancer Research, NCI, FDA, FNIH and 5 pharmaceutical companies[9].

At the Reagan-Udall Foundation, a public private partnership created by Congress to support regulatory science, post-marketing safety surveillance is being advanced via the Innovation in Medical Evidence Development and Surveillance project. Among other projects, a new predictive toxicology project designed to identify women at risk for adverse events during breast cancer therapy is being rolled out[10].

Venture capital investment in biomedical research has started to increase. PWC reported that biotechnology investment dollars rose 8 percent in 2013 to $4.5 billion going into 470 deals. However the percentage of all VC dollars invested in the life sciences sector fell from 25 to 23% in 2013 compared with 2012[11]. There has also been a recent boom in biotechnology IPO with 37 in 2013 and 24 in the first quarter of 2014[12].

These are encouraging signs but much more needs to be done if we are going to reach the ambitious goals set in PCAST report[1], maintain our global leadership position in life sciences and address the healthcare challenges that we now confront. I expect that all members of the ecosystem will continue to rise to these challenges but additional help and leadership from Congress could be tremendously beneficial.

Some specific areas for Congress to target are:

1) Clinical trials are the greatest cost driver of biologic and drug development. Today each clinical trial essentially requires establishing a new

infrastructure facilitating the creation of clinical trial networks involving academic investigators, patient advocacy groups and industry sponsors in close collaboration with FDA to increase cost efficiency, shorten time lines and allow more "plug and play" clinical studies. Examples to consider are the Clinical Trials Transformation Initiative/NIH Collaboratory project that has been established to support the design and rapid execution of several "Pragmatic Clinical Trial Demonstration Projects" including performing randomized trials using electronic health records[13, 14] and the Cystic Fibrosis Foundation's Therapeutic Development Network (TDN), the largest cystic fibrosis clinical trials network in the world[15] and the Lung Cancer Master Protocol established under FNIH[9]. Training of additional investigators Likewise establishment of national IRB's and Safety Monitoring Boards staffed with professional staff who are experts and have the time to dedicate to these critical endeavors may further reduce cost and time. More industry collaborations such as Transcelerate Biomedical[6] should also be encouraged so that industry can find ways to share data and reduce cost in development infrastructure and cost in noncompetitive areas. FDA's involvement in all these initiatives is critical.

2) Ensuring that FDA has adequate resources to do their job. Scientific advances are driving an explosion of new molecular and targeted "precision" therapies. Many of these will likely be used in novel combinations and along with new diagnostics and require sophisticated biomarkers to assess their

efficacy as early in the course of therapy as possible. Likewise we are on the threshold of new gene and regenerative medicine therapies. New trial designs and clinical endpoints designed to allow assessment of efficacy in smaller more targeted populations is also urgently needed to make it feasible to perform appropriate clinical studies. This will require collaborative efforts with academics and patient advocacy groups.

3) Likewise FDA must expand its science base accordingly, by recruiting scientists trained in the new disciplines, providing training for its current work force, expanding intramural Fellowship programs to ensure a continuous influx of contemporary expertise, not just for FDA but for the ecosystem at large. Intramural regulatory science programs should also be expanded to ensure that FDA scientists could continue to advance emerging field of regulatory science. Congress should ensure that FDA has appropriate recruiting resources and staff development programs in place, such as sabbaticals, the ability to attend scientific meetings and protected time for original research and scholarship for scientific staff.

4) An increasing share of biomedical innovation is originating in small companies. Often these companies have spectacular science but may lack the requisite knowledge of the regulatory pathway to advance their products expeditiously. Experience has taught me that a frequent interaction with FDA along the development path is a factor for success. FDA should be

funded to expand staff in every division so that more frequent and productive meetings can be supported. FDA should also be funded to create an outreach program to facilitate training of small companies on complex development pathways and guidances.

5) We must rely upon FDA's expertise benefit/risk assessment and clinical trials. Congress should therefore examine the statutes to ensure that FDA has the statutory flexibility and latitude to work with sponsors to design scientifically rigorous programs based on contemporary research methods to more rapidly and cost efficiently. The Breakthrough designation and the recently introduced ADAPT act (H.R. 3742) creating a targeted accelerated approval path for anti-infective drugs are excellent examples of regulatory enhancements that could speed life saving therapies to market. FDA should have the flexibility to be able to work with sponsors liberally in any therapeutic area of high need to undertake similar programs that will result in accelerated access. Use of Special Medical Use (SMU) approvals for appropriate products and indications could allow accelerated approval of medicines that might ultimately have broader use with restricted distribution. An analysis should be undertaken to assess whether FDA has sufficient statutory authority to allow this flexibility.

6) Examine policies that limit how genomic data can be used to inform drug safety assessment and clinical trials. Additional emphasis should be placed

on interpretation of mechanistic "evidence" to guide approval and treatment decisions when numbers are very small or n=1.

7) The NIH is the ultimate engine of innovation for the biomedical ecosystem. Congress must provide sustainable funding for the NIH that includes a steady year over year increase to increase the investigator pool, including better funding young investigators. Additional targeted funding to allow expanded collaboration between NIH and FDA as well as NIH and industry should also be appropriated.

8) Increased and sustainable funding for highly valuable public private partnerships, notable Reagan Udall Foundation should be appropriated to allow FDA to cost leverage and acquire access to external expertise as needed to support its scientific mission. Like FNIH the RUF can provide a cost efficient organizational infrastructure and neutral convening organization to manage projects and help provide tools valuable to FDA, without impinging on FDA's regulatory function. Adequate structural funding provided by Congress would allow RUF to work with FDA to identify and find funders for such projects.

9) Examine existing incentives for investment in biomedical research and new drug/biologic development. Innovative R&D requires substantial capital investment over a long period of time. There will always be more innovative

ideas than capital to fund it. Competition for resources is thus healthy for the ecosystem. However, targeted tax reform designed to encourage investment pre-revenue companies would be enormously beneficial to innovative early stage companies like Medgenics. It would also be useful to examine tax incentives designed to encourage R&D and commercialization of patent-based products in the US. A number of European countries, most recently the UK have introduced such plans[16]

Our company, like hundreds of other small, innovative companies, faces many of these challenges every day. Our scientists – like virtually all industry scientists I have had the honor to lead or know – are incredibly dedicated, driven and focused on curing disease and alleviating suffering. Their ingenuity and problem solving ability amazes me every day. We are making rapid progress in understanding the diseases we target and advancing therapies. We rely heavily upon collaboration with academic scientists who advise us and also upon the regulators who seek to understand and help us to find the path forward. We also rely heavily upon our investors, including our Board Chairman, Dr. Sol Barer, the founder and ex-CEO of Celgene. They risk their capital because they believe we will succeed.

Clearly there is no time or resource to spare. We weigh every decision and every experiment with the utmost care. We understand the implications for our people, our investors, the country – but most importantly, for the patients and their parents who are desperately waiting for cures.

I applaud the Committee for undertaking this effort in the sincere belief that it can result in positive change. Enlightened, science-driven policy will allow companies like Medgenics to succeed, put the next generation of transformational therapies in the hands of caregivers around the world and increase the competiveness and prosperity of our country.

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Mr. PITTS. The Chair thanks the gentleman.

Now recognize Ms. Radcliffe, 5 minutes for an opening statement.

STATEMENT OF SARA RADCLIFFE

Ms. RADCLIFFE. Chairman Pitts, Ranking Member Pallone, and Members of the committee, my name is Sara Radcliffe, and I am the executive vice president for health of the Biotechnology Industry Organization, BIO. I thank you for the opportunity to testify here today.

BIO is the world's largest trade association, representing over 1,000 biotechnology companies, academic institutions, and State biotechnology centers across the United States. BIO applauds Chairman Upton, Representative Diana DeGette, and the committee members for undertaking the 21st Century Cures Initiative to examine what steps Congress can take to accelerate the pace of discovering and developing cures. We are excited to work with you to keep America the innovation capital of the world.

We also applaud the committee for holding a hearing on the PCAST report on drug innovation. It is critical that even in an environment of budgetary constraint, we do not yield to global competition and lose the next generation of discoveries that could treat or cure the myriad of chronic and life-threatening diseases. From an emotional point of view, we have a duty to work to end the suffering these diseases cause. From an economic point of view, the U.S. can't afford to lose these advancements. Medicare spent over $100 billion in 2012 caring for individuals suffering from Alzheimer's Disease, and the expense is only going to increase. By 2030, almost one out of every five Americans, some 72 million people, will be 65 years or older. If we could delay the onset of Alzheimer's by just 5 years, we would save $50 billion per year. We have a national imperative to find new solutions, and this can only be accomplished if we all work together to create and defend policies that protect intellectual property, empower regulatory agencies to keep pace with science, encourage the development and adoption of modern approaches to drug development, promote a robust reimbursement environment, and continue to incentivize investment in scientific research.

The PCAST report noted that the overall efficiency of pharmaceutical R&D efforts has been declining steadily for more than 50 years. While there are many contributing factors, it is widely recognized that increasing timelines and costs associated with clinical trials are key issues. More efficient clinical trials will reduce barriers to market for safe, innovative medicines.

In 2012, BIO launched our clinical modernization initiative to address four priority clinical research-related issues, some of which were also highlighted in the PCAST report. First, the use of centralized institutional review boards to promote greater efficiency, consistency and qualify of ethical oversight for multicenter clinical trials. Next, improving the FDA qualification process for drug development tools, including biomarkers. Additionally, advancing efforts by patient advocacy networks, medical centers, healthcare providers and other stakeholders to develop clinical trial networks and collaborative partnerships that could realize greater efficiency,

consistency and quality in the conduct of clinical research. Finally, implementing a risk-based approach to clinical trial monitoring that leverages centralized data monitoring through electronic data capture systems can lead to significant efficiencies for clinical trial sponsors.

We would also like to applaud Congress for already having taken action of several of the PCAST recommendations with the passage of the Food and Drug Safety Innovation Act, FDASIA. For example, PCAST urged the FDA to expand the use of the accelerated approval pathway beyond the traditional areas of HIV, AIDS and oncology, and to be more open to the use of surrogate endpoints and intermediate clinical endpoints that are reasonably likely to predict clinical benefit, and that can be measured earlier in drug development, pending post-market confirmation. FDASIA encourages FDA to utilize the accelerated approval program more broadly, which may result in fewer, smaller or shorter clinical trials without compromising or altering the high standards of the FDA for the approval of drugs.

FDA's draft guidance on expedited programs will be very useful to sponsors, however, we encourage the Agency to further clarify the process for validating a novel endpoint, and for FDA to—and sponsors to discuss potential surrogate or clinical endpoints earlier in drug development. The PCAST report notes the drug developers have expressed frustration that it is difficult to get clear and timely answers concerning the accessibility of specific predictors for accelerated approval. Without such clarity, the risk of employing such predictors during the lengthy drug development process is often too great to justify a significant investment.

Finally, there has been interest in an expedited approval process for medicines used for small populations. We look forward to continuing discussions with the committee on this issue.

Thank you for the opportunity to share with you our ideas.

[The prepared statement of Ms. Radcliffe follows:]

TESTIMONY OF SARA RADCLIFFE
ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION
BEFORE THE U.S. HOUSE OF REPRESENTATIVES
ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH HEARING

21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation

MAY 21, 2014

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, my name is Sara Radcliffe and I am testifying on behalf of the Biotechnology Industry Organization where I serve as the Executive Vice President for Health. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO applauds the Committee for its 21st Century Cures initiative to examine what steps the Committee can take to accelerate the pace of cures in America. We are excited to work with you as you seek ways to keep our nation the innovation capital of the world.

I. Introduction

The Challenge of Chronic and Debilitating Disease

The importance of supporting biomedical research and innovation and the development of new therapies cannot be overstated. Today, we face increasing competition around the globe to overtake U.S. world leadership in biomedical innovation. Even in this time of budgetary constraint, it is crucial that we not allow this to happen. We cannot afford to lose the next generation of discoveries that address one of the nation's leading cost drivers – chronic and debilitating disease.

In 2014, the direct costs to American society of caring for those with Alzheimer's will total an estimated $214 billion, including $150 billion in costs to Medicare and Medicaid – the direct cost is projected to reach 1.2 trillion by 2050.[1] By 2030, almost one out of every five Americans – some 72 million people – will be 65 years or older.[2] Clearly, chronic disease increasingly will drive health care costs in the future. Already, almost 84 cents of every health care dollar is spent is to care for

[1] Alzheimer's Association. "2014 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia*, Volume 10, Issue 2 (2014). http://www.alz.org/downloads/Facts_Figures_2014.pdf.
[2] Alzheimer's Association. "2014 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia*, Volume 10, Issue 2 (2014). http://www.alz.org/downloads/Facts_Figures_2014.pdf.

individuals suffering from a chronic disease.[3] It is therefore a national imperative that we find new solutions. This can only be accomplished if we as a nation establish and defend policies that protect intellectual property, promote the effective transfer of new technology, empower regulatory agencies to keep pace with science, encourage the development and adoption of modern approaches to drug development, and continue to invest in scientific research.

The Challenge of Global Competition

We are facing unprecedented global competition to be the world leader in biomedical research. In 2008, China pledged to invest $12 billion in drug development,[4] and in 2011, the Chinese government named biotech one of seven industries that will receive $1.7 trillion in government funding over a five-year period.[5] The European Union's Innovative Medicines Initiative is pumping $2.65 billion into Europe's biopharma industry.[6] America has developed more cures and breakthrough medicines than any other country and is home to over 2,500 biotech companies. However, this is not a position that will be sustained without continued investment and policies focused on supporting and incentivizing the next generation of biomedical discoveries, treatments, and cures. Only by continuing to invest in the biomedical research and development ecosystem will we maintain global leadership, be in a position to increase U.S. jobs, and ensure that all Americans have access to the benefits of biomedical innovation.

The Challenge of Economic and Job Growth

Life science R&D and the biopharmaceutical industry provide high-wage jobs both at public research institutions and in the biotech companies located near centers of academic research. The indirect effects of increased research funding on regional economies are significant. For example, sponsored biomedical research directly generates jobs in the host institutions, and indirect and induced job creation in the region amounts to additional job growth. In fact, the nation's 1.6 million bioscience jobs support an additional 3.4 million jobs in the United States, resulting in a total employment impact of over 5.1 million jobs.[7]

Continuing this pattern of job creation is crucial and will require continued and renewed commitment to forward-thinking policies that will allow this to happen. This clearly is a particular challenge in the current budget climate, but we cannot

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[3] Anderson, Gerard. "Chronic Care: Making the Case for Ongoing Care." Robert Wood Johnson Foundation 2010. www.rwjf.org/content/dam/farm/reports/reports/2010/rwjf54583.
[4] Daverman, Richard. "China Launches "Mega Program" to Fund Drug Development." ChinaBio Today. 9 November 2008. http://www.chinabiotoday.com/articles/20081109.
[5] Buckley, Chris. "China to invest US$1.7 trillion over 5 years in "strategic sectors": US official." The China Post. 23 November 2011. http://www.chinapost.com.tw/business/asia-china/2011/11/23/323724/China-to.htm.
[6] Hodgson, John. "€2 billion IMI launched with European pharma." Nature Biotechnology 26, 717-718 (2008).
[7] Battelle Technology Partnership Practice. "Battelle/BIO State Bioscience Industry Development 2012." June 2012. http://www.bio.org/sites/default/files/v3battelle-bio_2012_industry_development.pdf.

afford not to take creative steps to meet that challenge.

II. Discovery

Funding for the National Institutes of Health (NIH)

It is imperative that our country continue to invest in scientific discovery and innovation. Federally supported biomedical research builds the foundation of scientific and clinical knowledge that is widely communicated and used to improve the development of diagnostics, treatments, and cures. The U.S. funds biomedical research primarily through the NIH, the world's premier biomedical research agency; there is no private sector alternative for much of the basic research that NIH supports. However, after nearly a decade of budgets below biomedical inflation, NIH's inflation-adjusted funding is close to 20 percent lower today than in FY 2003.[8] This is a short-term budget-driven approach that is sure to have long-term adverse consequences for all Americans.

Decreasing investment in NIH-supported research will significantly inhibit our nation's ability to make new scientific discoveries that could advance clinical and translational knowledge in how we prevent, diagnose, and treat disease. NIH-supported research also provides training for young researchers. These functions provide the foundation from which scientific findings can be transferred to the private sector. Industry will conduct further research to develop these early-stage discoveries into the next generation of treatments and cures. This collaborative ecosystem benefits all Americans, by producing life-saving and life-altering medical products and also helps create numerous direct jobs in biotech companies as well as indirectly creating jobs within laboratories and other entities that supply such companies.

Ensuring that NIH is well-funded is necessary to sustain the public- private collaboration that transforms biomedical discoveries into innovative treatments for patients.

National Center for Advancing Translational Sciences (NCATS): Opportunity to Engage Industry and other Stakeholders in Finding Solutions to Critical Scientific Barriers[9]

BIO has been actively engaged in conversations with NIH since the concept of creating a new institute focused on translational research was first presented by NIH's Scientific Management Review Board in December 2010. The stated mission of NCATS is "to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions." BIO supports

[8] Federation of American Societies for Experimental Biology. "Budget Cuts Reduce Biomedical Research." http://www.faseb.org/portals/2/PDFs/opa/5.16.13%20NIH%20Funding%20Cuts%202-pager.pdf.

[9] "NIH establishes National Center for Advancing Translational Sciences." NIH Press Release, 23 December 2011. http://www.nih.gov/news/health/dec2011/od-23.htm.

the overarching goal of NCATS and agrees with report language included in the FY 2012 appropriations and statements made by NIH that research initiatives undertaken by NCATS should not be duplicative of the research and development done by industry.

The primary metric for determining the ultimate success of NCATS will be whether its initiatives yield significant reductions in time and expenses in the development of new therapeutics, while expanding the terrain of promising novel targets and pathways, thus improving the delivery of the next generation of medicines to patients. For NCATS to achieve its goal to enhance the development of innovative medicines, it must develop partnerships and collaborations with industry, regulators (including FDA), principal investigators, life science investors, and patient organizations.

In 2012, BIO conducted a survey asking companies to identify research areas that would best serve to improve the process of researching and developing new medicines. The top five recommendations for NCATS research priorities were: identification/validation of biomarkers for predicting therapeutic response, development/validation of novel clinical trial designs, development of predictive preclinical efficacy testing methods/tools; development of predictive preclinical toxicity testing methods/tools and development of effective patient recruitment methods/tools. Success in advancing these research areas would help maintain a robust pipeline of potential breakthrough treatments and cures. Certainly, continued input from industry collaborators will enhance the chance of achieving a salutary outcome.

FDA Funding

Bringing a new drug, biologic, or diagnostic to market requires extensive research, including clinical trials, that may require a decade or more to complete. This risky, long-term investment by biotechnology firms and venture capitalists is predicated on working within an FDA regulatory framework that is predictable, consistent, and well-resourced, and that has the scientific capability necessary to evaluate the benefits and risks of novel products in a timely manner. It is imperative that FDA oversee the development and approval of innovative diagnostics, treatments, vaccines, and cures efficiently.

Nearly 25 cents of every consumer dollar spent in the United States—$1 trillion—is on a product or process regulated by the FDA, and it is critical to American economic health and competitiveness that the agency have the resources necessary to carry out its mission effectively and efficiently. An effective and efficient FDA is critical to encourage biomedical innovation to deliver treatments and cures.

BIO urges that Congress provide $2.784 billion in Budget Authority for FDA for FY 2015. This funding would ensure that FDA programs such as Advancing Regulatory Science, Oversight of Pharmacy Compounding, Supply Chain Traceability, and the Medical Countermeasures Initiative can keep pace with today's science and promote and protect public health. BIO recommends an investment of an additional $100

million in FDA's medical products programs, including a total of $528 million for the human drugs Program and $231 million for the biologics program. In addition, BIO strongly supports legislation that would prevent user fees from being sequestered in future years, as this would threaten FDA's ability to ensure patients get new treatments and cures at the earliest possible time.

III. Development

Leveraging modern advancements in molecular biology and genomics, biotechnology companies have pioneered innovative and life-saving treatments for patients worldwide. New therapeutic and diagnostic products are leading to significant improvements in the care of patients with serious diseases – in many cases providing the first approved treatment for a condition. However, as PCAST and others have noted despite significant investments in the discovery and development of modern therapies and treatments the overall efficiency of biopharmaceutical research and development efforts has been declining steadily for more than 50 years. While many factors have combined to cause this overall decline, it is widely recognized that the increasing timelines and costs associated with clinical trials are key contributors to this problematic trend.

In companion studies published by the Tufts Center for the Study of Drug Development (CSDD) and the U.S. Federal Trade Commission, the average cost of drug development was estimated to be between $802 million[10] and more than $1 billion,[11] respectively, with substantial variation observed by therapeutic category.[12] As a function of increasing development costs, biopharmaceutical R&D efficiency has declined approximately 80-fold over the last 60 years, with the number of new drug approvals per $1 billion spent on R&D decreasing by half approximately every 9 years since 1950.[13] The rising costs of drug development and the resulting decrease in R&D efficiency are complex, multi-factorial problems, but increased cost, complexity, and duration of clinical trials are widely accepted to be important contributing factors.[14,15] Illustrative of this was a study conducted by the Manhattan Institute, which observed that as much as 90% of the development costs for many drugs ultimately approved by FDA were incurred during their phase III clinical trials.[16] Additionally, the duration of the clinical phase of approvals for biopharmaceuticals has steadily increased, from an average of 4.6 years in 1990-

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[10] DiMasi J, Hansen R, and Grabowski H (2003) The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*. 22: 151-185.
[11] Adams CP and Brantner VV (2008) Spending on New Drug Development. *Health Economics*. 19, 130-141.
[12] Adams CP and Brantner VV (2006) New Drug Development: Estimating Entry from Human Clinical Trials. *Health Affairs* (2006) March/April, 420-428.
[13] Scannell JW, Blanckley A, Boldon H, and Warrington B (2012) Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews: Drug Discovery* 11, 191-200.
[14] Ruffolo RR (2006) Why has R&D productivity declined in the pharmaceutical industry? *Expert Opin. Drug Disc.* 1(2):99-102.
[15] Weatherall M (1982) An end to the search for new drugs? *Nature* 296, 387-390.
[16] Avik R (2012) *The Stifling Cost of Lengthy Clinical Drug Trials.* Manhattan Institute, available at http://www.manhattan-institute.org/pdf/fda_05.pdf .

1994 to an average of 7.1 years in 2005-2009.[17] Concomitant with the increase in clinical trial duration are rising protocol complexities and declining enrollment and retention rates.[18,19]

Confronting the problem of increasing costs and durations of clinical trials is a daunting task. The biotechnology industry is committed to partnering with Congress, FDA, NIH, patients, academia and other stakeholders to make meaningful progress toward improving the conduct of clinical trials. More efficient clinical trials translate to reduced barriers to market for safe, innovative medicines the ultimate goal of patients and industry.

Clinical Trial Modernization Initiative

With this goal in mind, BIO launched its Clinical Trial Modernization Initiative (CTMI) in 2012, based on the pillars of four initial priority issues, which were also highlighted in the PCAST report:

1. *Use of Centralized Institutional Review Boards (IRBs)*

Multicenter clinical trial protocols are most often subject to review by multiple, independent IRBs, which results in delays to study start-up, and inconsistencies in the quality and conduct of ethical review. Centralized IRBs (cIRBs) promote greater efficiency, consistency, and quality of ethical oversight for multicenter clinical trials.

2. *Improving the FDA Qualification Process for Drug Development Tools*

Drug Development Tools (DDTs), including biomarkers, patient reported outcome tools, and novel clinical trial designs, have the potential to improve public health and yield major impacts on the efficiency of drug development programs and their regulatory review. Despite this enormous potential, and a commensurate expenditure of resources, very few DDTs have been successfully qualified. Increasing the efficiency of the FDA qualification process for DDTs could greatly benefit the innovation ecosystem, enabling life-saving therapies to be delivered to patients more expeditiously.

3. *Promotion of Clinical Trial Networks and Partnerships*

Traditionally, in the United States and globally, there has been no established, enduring clinical trials infrastructure. This leads to considerable, unnecessary costs related to study start-up, enrollment, investigator training, and site certification. Advancing efforts by patient advocacy networks, medical centers, health care providers, and other stakeholders to develop clinical trial networks and collaborative partnerships could result ingreater efficiency, consistency, and quality

[17] Tufts Center for the Study of Drug Development (12 April 2010) *PDUFA V Public Meeting.*
[18] Allison M (2012) Reinventing clinical trials. *Nature Biotechnology* 30(1):41-49.
[19] Tufts Center for the Study of Drug Development (2008) Growing protocol design complexity stresses investigators, volunteers. *Impact Report* 10(1).

in the conduct of clinical research and improve the feasibility of clinical trials for special populations.

4. Risk-Based Approaches to Clinical Trial Monitoring

For many pharmaceutical and biotechnology companies, the predominant mechanism to monitor the progress of clinical investigations involves frequent visits to each clinical investigator site to evaluate study conduct and review data for each enrolled subject. Implementation of a risk-based approach to clinical trial monitoring that leverages centralized data monitoring through electronic data capture systems can lead to significant efficiencies for clinical trial sponsors.

BIO is driving change in these priority issue areas by facilitating industry adoption of best-practices, creating strategic partnerships, and advocating for policies to reduce regulatory barriers. We welcome the chance to work with the Committee to advance progress on these important initiatives.

Expansion of Accelerated Approval

Congress has already taken action on several PCAST recommendations through passage of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). For example, PCAST urged FDA to expand the use of the Accelerated Approval pathway beyond the traditional areas of HIV/AIDS and oncology and to be more open to the use of surrogate endpoints and intermediate clinical endpoints that are reasonably likely to predict clinical benefit and can be measured earlier in drug development pending post-market confirmation. FDASIA encourages FDA to utilize the Accelerated Approval program more broadly, which "may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs." BIO is closely tracking Accelerated Approval statistics to understand better how the modernized pathway is being embraced by FDA and which disease areas are benefiting.

While FDA's draft guidance on FDA's Expedited Programs is welcome, we encourage the Agency to clarify further the process for validating a novel endpoint and for FDA and sponsors to discuss potential surrogate or intermediate clinical endpoints earlier in drug development. The PCAST report notes that "Drug developers have expressed frustration that it is difficult to get clear and timely answers concerning the acceptability of specific predictors for Accelerated Approval. Without such clarity, the risk of employing such predictors during the lengthy drug development process is often too great to justify significant investment." A lack of process predictability and criteria for developing novel surrogate endpoints can to undermine the program. We will work with FDA to establish clear evidentiary criteria to support the use of a particular surrogate endpoints or biomarkers.

Breakthrough Therapy Designation

FDASIA also established a Breakthrough Therapy Designation process, which has received considerable interest by industry and FDA alike. FDA has designated more than 40 products as "Breakthrough Products" that demonstrate substantial improvements over existing treatments based on early-stage clinical evidence. FDA has approved four of these products to date. By leveraging increased FDA-sponsor coordination and senior, cross-disciplinary involvement to identify the most efficient drug development strategies, drug development times can be reduced substantially. In addition, it is also important that FDA and sponsors work together to reduce non-clinical development bottlenecks, such as scale-up and validation of manufacturing processes, and to ensure timely review of companion diagnostics and combination products.

Timely, Interactive Communication during Drug Development

The PCAST report also states that the "[-D]rug sponsors benefit from clear and frequent communications with the FDA about their specific projects from the earliest stages through final review. Clear and consistent answers are important because they help companies avoid costly mistakes in designing a project. Rapid answers are important because they avoid expensive delays; this is particularly important for small companies, which often have a single product in development, a high burn rate and limited capital. There are many challenges in optimizing the communication between drug sponsors and the FDA."[20] Under PDUFA V, FDA committed to a philosophy that timely interactive communication with sponsors during drug development is a core Agency principle. By identifying best practices for FDA-sponsor communication, training reviewers on those practices, and staffing a liaison office to help facilitate FDA-sponsor communication, the agency is taking important steps to improve scientific communication during drug development and reduce unnecessary delays related to miscommunication. The scientific method does not operate in a vacuum, and we encourage FDA to continue to emphasize the importance of interactive scientific discourse during drug development.

Special Medical Use

PCAST, FDA, and other stakeholders have called for the establishment of a "Special Medical Use" pathway to encourage the development of therapies for serious manifestations of more common conditions, such as antibiotic resistant pathogens. We applaud Representatives Gingrey (R-GA) and Green (D-TX) on their work on this issue and stand ready to help articulate a voluntary SMU designation process that can help foster novel drug development while not infringing on the practice of medicine.

Patient Focused Drug Development

The PCAST report notes that "patients themselves have played a critical role in propelling advances by focusing attention on the urgency of developing therapies and spurring creative approaches, and by participating in clinical trials." BIO fully

[20] PCAST, p. 44

agrees that FDA's drug evaluation process should be appropriately guided by patient perspectives on unmet medical need, the adequacy of existing therapies, anticipated benefits from new treatment options, and tolerance for potential risks.

Under PDUFA V, patient advocates, industry, and FDA have embraced this patient-centric approach to innovative drug development. For example, FDA's new Patient Focused Drug Development (PFDD) program is soliciting views from patient constituencies through meetings on various disease areas to incorporate patient perspectives into regulatory decisions and to help inform future drug development approaches.

The implementation of FDA's new Structured Benefit/Risk framework will also help to ensure that benefits and risks are evaluated the context of unmet medical need and the body of available scientific knowledge so the balance of these factors can be understood more clearly and consistently within FDA and by external stakeholders.

Management Practices at FDA

PCAST's Recommendation #7 is "Reform Management Practices at FDA". BIO has made a number of recommendations in this regard. For example, we have suggested that in addition to stating FDA's critical responsibility to protect the public, the Agency's mission statement should include a clear mandate to encourage the development and advancement of innovative products. This will empower FDA to enhance its capacity commitment to incorporate the latest scientific advances into its decision-making processes.

We have also suggested that an FDA Management Review Board be created to help FDA keep pace with its increasing responsibilities and the latest scientific advances. On a periodic basis and at the request of the FDA Commissioner, the Management Review Board would provide the Commissioner with fresh, visionary, and independent thinking from external experts and FDA thought leaders on how to improve the ability of the Agency to carry out its mission.

We also have suggested that a new position be created at FDA, the Chief Innovation Officer, whose charge would be to ensure that innovative tools and approaches are integrated into FDA review processes, to enhance timely and efficient review and to incentivize the development and utilization of modern scientific approaches to research and development.

IV. Delivery

Post-Market Real-World Data

Advancements in information technology and the adoption of electronic health records places biomedical sciences at the cusp of fully realizing a "learning healthcare system" that can evaluate real-world data to assess the safety and

efficacy of medical interventions, including drugs and biologics, to support the cycle of biomedical innovation. While most randomized, controlled clinical trials can readily identify higher-frequency adverse events and assess clinical efficacy, they must enroll tens of thousands of patients to be powered sufficiently to detect rare adverse events or slowly progressing clinical manifestations. Further increasing the size, length, and complexity of clinical trials is economically unsustainable and places further burdens on the ability of researchers to feasibly enroll and conduct clinical trials.

Rather, we should pursue approaches that more closely integrate reasonably sized pre-market clinical studies with mandatory post-market surveillance and analysis of real-world electronic data to assess safety and efficacy further and to refine the therapy's benefit/risk profile. For example, marketing approval could be granted on the basis of a demonstration of safety and efficacy in a highly targeted patient population (that would require fewer patients in clinical trials) with analysis of electronic health record data and "virtual" clinical studies to support expanded indications in a post-market setting. As part of the Agency's Sentinel Network initiative, FDA has made considerable progress in developing the tools and methodologies for assessing post-market data to identify safety signals; we should continue to build upon that foundation. While the scientific methods in this area continue to evolve, we must embrace a future where we can better leverage real-world data to answer key research questions more efficiently than in large-scale clinical trials.

Reimbursement

While improvements in the discovery and development of medical products are critically important in the bench-to-bedside continuum, patients must be able to access the products or those improvements will be meaningless. Predictable and transparent payment and coverage policies are critical to ensuring that these treatments and cures get to the patients who need them most. As a representative of an industry committed to discovering new cures and ensuring patient access to them, BIO closely monitors changes to how our member's products are covered and paid for. Proposals that limit access to novel medical therapies and technologies can lead to potential delays in obtaining care, or sub-optimal care, resulting in higher health costs and poor health outcomes.

Innovations such as new medical therapies can reduce the burden of, or even cure, costly diseases, as well as keep total societal costs down. However, increasingly we hear from the private investors that fund our smallest companies that reimbursement uncertainty is forcing them to look to alternative investments – not just different companies, but different, unrelated industries, all together. BIO's primary goals are to ensure that patients have access to appropriate therapies and to protect the incentives needed to develop breakthrough medicines to treat the patients of tomorrow. The principles that guide our work in this area are the following:

- Quality: Protect high quality care. Payment reform models must focus on the quality of care delivered, not narrowly on lowering the cost of care.
- Patient Impact: Any proposed payment system reforms must integrate a "patient impact" assessment into their development.
- Access: Protect patient access to appropriate therapies, drug delivery devices, diagnostics and vaccines.
- Adherence: Support patient adherence to therapies.
- Innovation: Maintain incentives to develop breakthrough therapies to address patients' unmet needs and to discover the cures of tomorrow. The research and development of new cures and breakthrough therapies must be a high priority of our nation's health care system – a system that pays for health, wellness and innovation.
- Evidence: Ensure that sound evidence is used for payment policy changes.
- Transparency: Ensure sufficient stakeholder input through a transparent, predictable and inclusive process.
- Adequate Reimbursement: New payment models should not be undertaken without comprehensive evidence that such changes will improve outcomes while lowering overall costs and must place central priority on ensuring access to quality patient care and improving outcomes.

V. Conclusion

BIO appreciates the opportunity to talk with the Committee today, and looks forward to working with you on this important initiative.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognizes Mr. Sasinowski, 5 minutes for his opening statement.

STATEMENT OF FRANK J. SASINOWSKI

Mr. SASINOWSKI. Thank you for inviting me to testify.

I would like to introduce my colleagues, Alex Verone and James Valentine, who helped me prepare this testimony.

My testimony draws on 31 years of aiding new medicines get to patients in need. My career started at FDA in 1983, and I have a special passion for helping on therapies for rare diseases, because both my son and I have rare diseases. And I have been on the Board of Directors of NORD for the past 14 years. I am here today representing both myself and NORD. NORD, for over 40 years, has been the voice for the 30 million Americans with rare diseases.

I will be presenting 4 proposals for you to consider. My first proposal is for FDA to adopt a practice of considering the appropriateness of accelerated approval for each new therapy. Both PCAST and FDASIA exhort FDA to use its accelerated approval authority more. Last September, Alex Verone and I submitted to FDA our 65-page analysis of FDA's accelerated approvals. Our analysis shows that FDA knows how to use this authority, and even how to use it flexibly, creatively and nimbly. In my view, what is needed now is simply to give this accelerated approval pathway greater visibility, so that it will be used more frequently for the benefit of patients, as was recommended by both PCAST and FDASIA.

So my first proposal is for this committee to encourage FDA to consider whether accelerated approval is appropriate for every new drug therapy that is brought by sponsors to the FDA.

My second proposal is for sponsors and FDA to use intermediate clinical endpoints, also known by its acronym of ICE, more often to secure accelerated approval. Alex and I analyzed the FDA accelerated approval precedents according to the 3 major factors that FDA described in the document that Ms. Radcliffe just mentioned, its June 2013 FDA guidance on expedited approvals. We analyzed the FDA approvals according to these three factors, and we found that two of these three factors are far less relevant to accelerated approvals, when accelerated approvals based on intermediate clinical endpoints or ICE, rather than surrogate endpoints. Therefore, the quantity of evidence that sponsors must acquire and present to FDA, and that FDA then must review, may be substantially reduced if more accelerated approvals are based on intermediate clinical endpoints or ICE.

So to get more medicines to patients faster, this committee should encourage both sponsors and FDA simply to use more ICE.

My third proposal is to tap into the statutory authority for approving drugs that Congress created and gave to FDA in the 1997 FDAMA Law. This authority stated that FDA could approve a drug based on a single study with confirmatory evidence. Congress created this as an alternative to the standard Congress created in 1962, which has generally been interpreted to require two studies. This 1997 alternatives authority has been almost universally overlooked by all stakeholders, academia, sponsors, patients and even largely by the FDA as well.

I now ask my colleagues to hold up a chart. This chart is in my written testimony in greater detail, but this committee could propose that this simple chart be used at FDA Advisory Committee, and other FDA sponsor meetings and at other forums to ensure that all the existing authorities are considered by every stakeholder for every new drug. Notice that the second line identifies that 1997 statutory authority or standard of a single study with confirmatory evidence, and the fourth line ensures that all recognize the potential of accelerated approval. So this one simple chart could help accomplish both of my first and third proposals.

Thank you, James and Alex.

My fourth proposal is for the committee to encourage FDA to issue guidance on cumulative distribution analyses of clinical study results. This could help understand the clinical meaningfulness of a new therapy. PCAST recommended that FDA issue more guidances to communicate innovative advances and regulatory science just like this one of cumulative distribution analyses.

So I am deeply honored by you to have been asked to appear before you today. Thank you.

[The prepared statement of Mr. Sasinowski follows:]

Frank J. Sasinowski, M.S., M.P.H., J.D.

Director, Hyman, Phelps & McNamara, P.C.

Director, National Organization for Rare Disorders

Testimony – Committee on Energy and Commerce

Subcommittee on Health

Tuesday, May 20, 2014

21st Century Cures Initiative & Examining PCAST

to Advance Developing Medicines for Americans

Thank you for this opportunity to provide input on several important PCAST recommendations that may have implications for the 21st Century Cures initiative. As a member of the Board of Directors of the National Organization for Rare Disorders (NORD), and because I have a rare autoimmune disease for which there is no approved therapy, and because none of the approved therapies for Tourette Syndrome work for my son Tom, I am reminded daily that the 30 million Americans affected by rare diseases as well as all of our families have a vital and urgent need for faster development of therapies for each of "us." In addition to my more than three decades of experience in drug regulation, I was involved with the President's Council of Advisors on Science and Technology (PCAST) report that is being discussed today. With that as background, let me present you with 4 proposals for the Committee and Subcommittee to consider as you move forward with your 21st Century Cures initiative.

The 21st Century Cures "Call to Action" states that one way for Congress to reach its objective of helping to accelerate the discovery, development, and delivery of promising new treatments is for Congress to ensure that existing statutory and regulatory authorities are being

used to their maximum potential. Toward meeting this objective, I present 4 proposals that build on recommendations in the PCAST report and which the 21st Century Cures initiative could consider using to propel drug development and yield, both quickly and with little new effort, great benefits for patients. While new, more explicit statutory authority from Congress could direct FDA to adopt these (or other) concepts, the Agency, under current law, has sufficient authority to accomplish these things now. However, this Committee and your 21st Century Cures initiative still has a vital role to play in that this Committee has the power to assure FDA that its or the Agency's expanded exercise of existing authorities, as I propose, is encouraged by both sides of the aisle. This is because the PCAST and my proposals for expanded use of current authorities is quintessentially bipartisan in that those suffering with disease are, first and foremost, patients in need of that help, and disease has no political affiliation or partisanship.

Proposal #1: Increase the Visibility and Use of Accelerated Approval by Considering it for Each New Therapy.

Both PCAST and FDASIA recommended that FDA expand, beyond cancer and AIDS, use of its Accelerated Approval authority to approve medicines for those with serious diseases and no available therapies. My September 2013 analysis of the 19 therapies approved since 1992 (when FDA created Subpart H) shows that FDA has already been exercising considerable, reasonable flexibility in using this approval authority. This means that to implement the PCAST and FDASIA recommendation to use this authority more often, FDA would not need to establish any new program or policies, but may only need to give this approval pathway more visibility and more frequent consideration. My first proposal is that Congress encourage FDA to adopt a practice of considering the appropriateness of its Accelerated Approval authority for each new therapy. One way to accomplish this would be to have FDA and a sponsor consider whether that therapy could be a candidate for this approval pathway at one or more key FDA Sponsor

meetings such as pre-IND, End-of-Phase 2, pre-NDA/BLA and Advisory Committee meetings. This simple change would require nearly no resources or time, but could have a huge impact on Americans' access to medicines for serious diseases. Also, see Proposal #3 below.[1]

The PCAST report recommends that FDA use more often FDA's existing Accelerated Approval authority, what is also known as Subpart H or Fast Track. The PCAST report noted that 87% of Subpart H approvals had been for cancer, HIV or anthrax. Since 1992, only 21 therapies have been approved via Accelerated Approval authority were for indications other than cancer or HIV.

Specifically, the PCAST report stated:

> "The FDA should make fuller use of authorities previously granted by legislation and not yet fully utilized. The FDA should expand the use in practice of its existing authority for Accelerated Approval. FDA should direct its staff, across all divisions, to make full use of the Accelerated Approval track for all drugs meeting the statutory standard of addressing an unmet medical need for a serious or life threatening illness and demonstrating an effect on a clinical endpoint ... or on a surrogate endpoint that is reasonably likely to predict clinical benefit."[2]

At about the same time as the PCAST report,[3] Congress and President Obama in FDASIA recognized the need for expanded use of the Accelerated Approval pathway and revised the statutory provisions of Accelerated Approval to "encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."[4]

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1 A chart is proposed which is attached as Appendix 1.
2 PCAST Report at p. 61 (emphasis added).
3 The PCAST report issued in September 2013 and FDASIA became law in July 2013.
4 Federal Food, Drug, and Cosmetic (FDC) Act § 506(e)(1).

In June 2013, FDA released its *Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics* (Draft Guidance). The Draft Guidance lists and describes factors that FDA views as critical to Accelerated Approval.

Given this renewed recognition of the promise of FDA's Accelerated Approval authority to address those suffering from serious diseases without adequate available therapy, and given FDA's issuance of its Draft Guidance addressing the Agency's Accelerated Approval authority, my colleague Alexander Varond and I conducted an analysis of FDA precedents in order to promote a better understanding of the circumstances under which Accelerated Approval may be employed in order: (1) to facilitate the development and expedited review of new drugs with the potential to address unmet needs for serious and life-threatening illness; and (2) to mobilize expanded use of Accelerated Approval, consistent with PCAST and FDASIA.

The linchpin of the Accelerated Approval authority is the concept that a showing on a surrogate or intermediate clinical endpoint (ICE) may be sufficient for meeting the statutory criterion or standard of "substantial evidence" of effectiveness.

There have been many misunderstandings, in my view, of this Accelerated Approval authority. Some have thought that this means that the quantum or quality of evidence was somehow reduced, and the statutory requirement of "substantial evidence of effectiveness" was in some way, in whole or in part, reduced, skirted or deferred. While this is not the case in statute, regulation or policy, the other extreme is just as likely not to "serve the public well."[5] The other extreme is the view that unless the surrogate is validated, it cannot be relied upon in an Accelerated Approval decision. This is sometimes found in FDA reviews that conclude that the Sponsor's evidence failed to satisfy the standard of approval because the trial(s) attempted to

[5] PCAST Report at p. 59.

both prove the drug's effect on the surrogate as well as prove the clinical benefit, and the clinical benefit showing was not robust enough to confirm or validate the drug's effect on the surrogate.

Between these two extremes, there has existed a gaping hole that has begged to be addressed for nearly three decades and that hole is this:

- What is the foundation for FDA's determination that the evidence of effectiveness is capable of supporting an Accelerated Approval?

My colleague Alexander Varond and I reviewed, based on examination of publicly available information, the strength of the scientific and clinical evidence for evaluation of the particular factors that the FDA considers in approving a drug under its Accelerated Approval authority. Our analysis showed that FDA has exercised considerable flexibility in the therapies it has approved under Accelerated Approval.[6] In all, 19 non-AIDS, non-cancer Accelerated Approvals were identified and analyzed. AIDS and cancer therapies were excluded from the analysis because there is comparatively greater regulatory certainty associated with Accelerated Approvals for these two therapeutic areas.

Our study was designed to assess the evidentiary foundation for FDA's determinations that an unvalidated surrogate or clinical endpoint was "reasonably likely to predict" patient benefit sufficient to meet the statutory standard of "substantial evidence of effectiveness." Let me explain how we conducted this analysis.

The FDA's June 2013 Draft Guidance identified the following as the three most important factors in FDA's reaching its Accelerated Approval decisions: (1) understanding of

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[6] E-Filing on Regulations.Gov by Frank Sasinowski and Alexander Varond, Hyman, Phelps & McNamara, P.C. re: Docket No. FDA-2013-D-0575, Comment on Section VII. C.: "Evidentiary Criteria for Accelerated Approval" of the FDA "Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics" (Aug. 26, 2013), available at http://www.regulations.gov/contentStreamer?objectId=09000064813ca6cb&disposition=attachment&contentType=pdf (Appendix 2). Manuscript in development for publication with update that will expand the analyses.

the disease process; (2) understanding of the relationship between the drug's effect on the surrogate or ICE and the disease; and (3) strength of clinical evidence, with strength of clinical evidence broken into two subcategories: strength of clinical evidence on the surrogate endpoint or ICE, and strength of clinical evidence on the clinical benefit.

Our study analyzed all the relevant FDA reviews according to each of these 3 factors. What now follows is a summary of the findings of our analysis, broken down according to those 3 major FDA factors.

The first factor is the understanding of the disease, because, as FDA explains, a clear understanding of the pathophysiology of the disease process will facilitate reliance upon a surrogate or ICE.[7] However, our analysis found that the absence of a complete understanding of the disease process or even the existence of a relatively weak understanding of the disease process is not, in and of itself, incompatible with an FDA decision to grant an Accelerated Approval. So, with respect to the application of this factor that FDA identified as critical to its decision on Accelerated Approval, FDA exhibited flexibility, according to the findings of our analysis, in applying this consideration to the evidence presented. Figure 1, below, illustrates the strength of FDA's understanding of the disease process for each of the 19 drugs.

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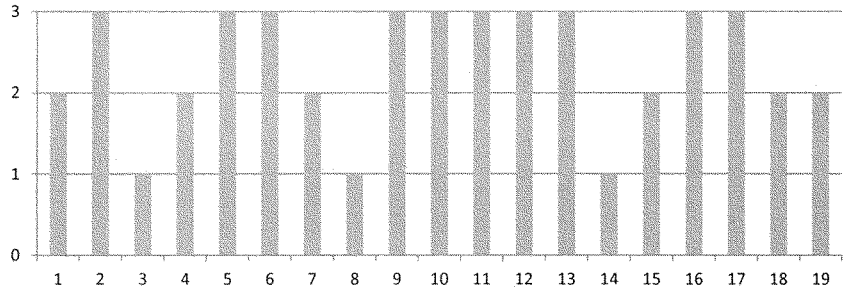
[7] Draft Guidance at pp. 18-19, lines 617-648.

Figure 1: Understanding of the Disease Process (0-3)*

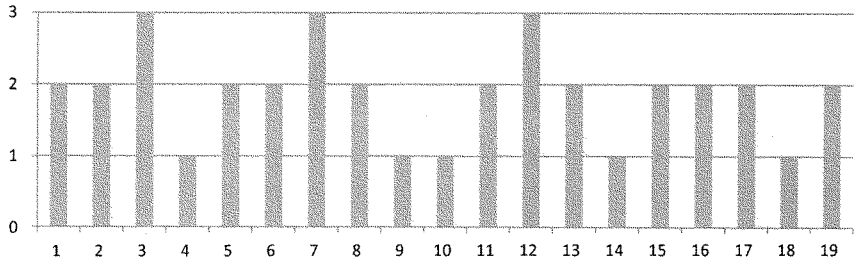


* 1. Sirturo; 2. Ferriprox; 3. Makena; 4. Promacta; 5. Exjade; 6. Levaquin; 7. Tysabri; 8. Luveris; 9. Fabrazyme; 10. Remodulin; 11. Cipro; 12. Celebrex; 13. Synercid; 14. Remicade; 15. Priftin; 16. Sulfamylon; 17. ProAmatine; 18. Biaxin; 19. Betaseron

The second key factor listed by FDA in its Draft Guidance is how well-understood the relationship is between the drug's effect on the surrogate or ICE and the disease process.[8] Our study showed that, in several cases, there was only relatively weak support for the relationship between the surrogate and the disease process, such as in the case of Fabrazyme (where there was little evidence on the relationship between clearance of substrate in particular cell types and progressive deterioration of renal function). Again, a weaker showing in this particular factor was not a bar to Accelerated Approval, so here too FDA exhibited flexibility. Figure 2, below, illustrates the strength of the understanding of the relationship between the drug's effect on surrogate and the disease for each of the 19 drugs.

[8] *Id.* at p. 19, lines 653-675.

Figure 2: Understanding of the Relationship between the Drug's Effect on Surrogate and the Disease (0-3)*



* 1. Sirturo; 2. Ferriprox; 3. Makena; 4. Promacta; 5. Exjade; 6. Levaquin; 7. Tysabri; 8. Luveris; 9. Fabrazyme; 10. Remodulin; 11. Cipro; 12. Celebrex; 13. Synercid; 14. Remicade; 15. Priftin; 16. Sulfamylon; 17. ProAmatine; 18. Biaxin; 19. Betaseron

In its Draft Guidance, FDA noted the critical role of the clinical strength of evidence of the drug both on the surrogate or ICE and on the clinical benefit as well, and our analysis below breaks this into these two separate sub-analyses. While FDA was not able to articulate generalizable principles with respect to the strength of clinical evidence,[9] the power of our analysis is that by looking at the specifics of each of the 19 precedents, our analysis was able to ascertain that which may otherwise not be discernible.

With regard to strength of clinical evidence on their surrogates or ICEs, even therapies such as Sulfamylon, which had very weak strength of clinical evidence on its endpoints, was judged by FDA as appropriately qualified for Accelerated Approval, carried mainly on the strength of the evidence on other factors.

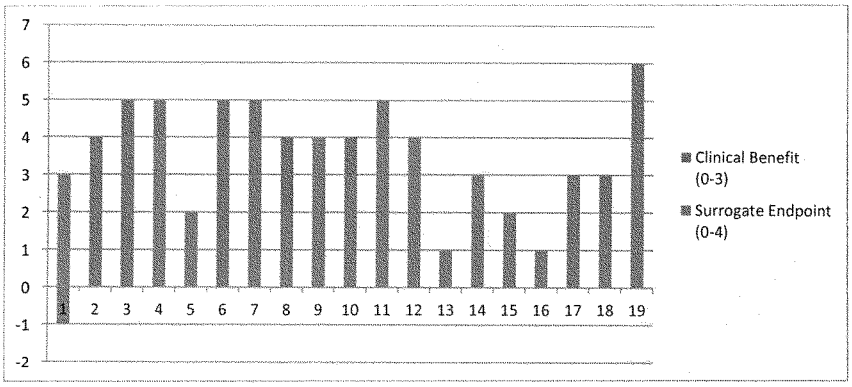
The second half of the assessment of overall clinical evidence was the strength of evidence of clinical benefit. It was not anticipated that these scores would be high for this factor, and generally the Accelerated Approval precedents had relatively little clinical evidence of

[9] *Id.* at p. 18, lines 614-615.

benefit in the clinical data sets that were the basis for approval. Ten of the 19 precedents had essentially no substantial positive evidence of clinical benefit, and one of the precedents actually had a fairly strong negative numerical "lean" in clinical outcome evidence, suggesting that the therapy may have a negative impact on long-term clinical benefit.

Overall, our analysis shows that FDA was flexible in applying this third major factor to these Accelerated Approval precedents, just as FDA has with respect to the first two major factors. Figure 3, below, illustrates the strength of clinical evidence on both the surrogate/ICE and the clinical benefit for each of the 19 drugs.

Figure 3: Strength of Clinical Evidence (0-7)*



* 1. Sirturo; 2. Ferriprox; 3. Makena; 4. Promacta; 5. Exjade; 6. Levaquin; 7. Tysabri; 8. Luveris; 9. Fabrazyme; 10. Remodulin; 11. Cipro; 12. Celebrex; 13. Synercid; 14. Remicade; 15. Priftin; 16. Sulfamylon; 17. ProAmatine; 18. Biaxin; 19. Betaseron

As with my prior analysis of FDA's orphan drug precedents,[10] this analysis of FDA's Accelerated Approval precedents testifies to FDA's flexibility in applying this Accelerated

[10] Frank Sasinowski, *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloging FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders*, 46 Drug Information Journal 238 (Mar. 2012) (Appendix 7).

Approval authority to therapies under FDA review. Robust compliance with all three major factors cited in FDA's Draft Guidance has not been required. Our analysis shows that FDA can exercise and has exercised substantial flexibility in applying the Accelerated Approval authority. Therefore, to embrace the mutual recommendations of PCAST and FDASIA for FDA to use this approval authority more will not require FDA to generate any new policies or procedures, nor will it require Congress to create and confer new authority, because it is my view that increased visibility and consideration of the Accelerated Approval pathway may achieve the desired result.

My proposal for achieving this increased visibility and consideration is a simple one: FDA could adopt a practice of considering whether each new therapy may be a candidate for Accelerated Approval. This could be considered at one or more of the key FDA/Sponsor interactions (that is, at the pre-IND, the End-of-Phase 2, the pre-NDA/BLA, and Advisory Committee meetings). Even though Sponsors have the option to request Fast Track designation, Sponsors and FDA have generally focused on traditional approval and therefore, Accelerated Approval has often not been considered. For instance, at two advisory committees I am familiar with (i.e., tolvaptan for autosomal dominant polycystic kidney disease in August 2013 and pirfenidone for idiopathic pulmonary fibrosis in March 2010),[11] the Accelerated Approval pathway was not discussed, even though both of these diseases are very serious and there were no therapies approved for either disease, and these considerations are the twin eligibility criteria for considering the Accelerated Approval pathway. In one way, my proposal is consistent with that part of the FDA Draft Guidance that encourages Sponsors who may be considering using an ICE in a program targeting Accelerated Approval to come in and discuss this approach with

[11] The publication of the results of a new trial on that day for this disease just were released on Sunday, May 18, 2014. King et al., *A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis*, N. Eng. J. Med., NEJM.org DOI: 10.1056/NEJNMoa1402582 (May 18, 2014) (Appendix 3).

FDA very early in the clinical development program.[12] Importantly, adoption of this proposal would not require enactment of any new statutory authority, nor would it impose anything more than a de mininis review of the potential qualification of each therapy for Accelerated Approval, that is, whether the disease being addressed is serious, and, if it is serious, then whether there already exists available therapy for that disease. Both of these are usually not difficult to discern. So the actions necessary to enable this proposal to be implemented are not heavy for Congress, FDA or Sponsors, and yet, the potential for expanding the use of Accelerated Approval by this simple measure are palpable.

Proposal #2: Using ICE more may Increase the Number of Accelerated Approval therapies.

PCAST recommended that FDA consider using Intermediate Clinical Endpoints (ICE) more often for Accelerated Approvals. Alex Varond and my (see above) was based on the 3 major factors in FDA's June 2013 Draft Guidance. It is my view that 2 of these 3 major factors would be significantly reduced in the FDA's review process if FDA and sponsors shifted to use ICE instead of unvalidated surrogates. Therefore, my second proposal is for Congress to encourage FDA and Sponsors to use ICE more often which would, according to our analysis, help FDA by reducing the demands of FDA's review of therapies under Accelerated Approval, and this may yield greater numbers of therapies approved by this pathway.

Intermediate clinical endpoints (ICE) present a largely untapped opportunity for Accelerated Approval. As mentioned in PCAST and in the FDA Draft Guidance, the use of ICE for Accelerated Approvals has been limited.

When FDA approves a therapy under Accelerated Approval using ICE instead of an unvalidated surrogate, FDA reduces the criticality or significance of two of the three factors

[12] Draft Guidance at p. 17, lines 580-582.

FDA considers in its Accelerated Approval decisions: both the need to have a clear understanding of the disease as well as the need to establish the relationship between the Accelerated Approval endpoint and the disease.

FDA's February 18, 2014 Accelerated Approval of Northera, the most recent Accelerated Approval, provides a helpful example.[13] Northera was approved for the treatment of "orthostatic dizziness, lightheadedness, or the 'feeling that you are about to black out' in adult patients." Northera was approved on trials that relied upon an ICE, specifically: a short term benefit or acute improvement on dizziness, which is the main symptom and disability of the disease. By relying upon this ICE for this approval, FDA could have greater confidence that the confirmatory Phase 4 study will likely be able to establish the durable or chronic continued benefit in the long term of that same symptom improvement that was shown in the acute setting and was the basis for this Accelerated Approval. Because the ICE in this case is the ultimate clinical benefit but merely in an acute setting, understanding of the disease process and understanding of the relationship between the drug's effect on the Accelerated Approval endpoint and the disease were less important in this case than in Accelerated Approval decisions that rely on an unvalidated surrogate as the endpoint. In other words, because the primary endpoint of short term dizziness (i.e., the ICE) is the same primary endpoint that will be tested in the confirmatory Phase 4 study but will need to be shown that this benefit is sustained in a chronic setting (i.e., the ultimate clinical benefit), the degree of regulatory uncertainty is reduced relative to an approval

[13] In addition to Northera, other examples of Subpart H approvals on ICE include Tysabri (ICE: decrease in relapse rate over the course of one year, clinical benefit: decrease in relapse rate over two years), Makena (ICE: reduction in preterm birth defined as less than 37 weeks, clinical benefit: improvement of infant outcomes, including death), Remodulin (ICE: combined exercise/Borg score analysis, clinical benefit: time to first occurrence of death, hospitalization for complications of pulmonary hypertension, need for esprostenol, or other clear evidence of deterioration), and Remicade (ICE: Clinical response defined as a reduction from baseline in the Crohn's Disease Activity Index Score of at least 70 points at the 4-week evaluation, clinical benefit: maintaining a sustained clinical outcome in patients with moderately to severly active Crohn's disease).

based on an unvalidated surrogate, and therefore the amount of evidence needed for these two factors— of understanding the disease and understanding the relationship between the endpoint and the disease— is lessened.

FDA's April 2003 approval of Fabrazyme for Fabry disease provides an illustrative counter-example. Fabrazyme was approved under Accelerated Approval but relying upon evidence of the drug's effect on an unvalidated surrogate: reduction of an intracellular substrate accumulation in the vascular endothelium. In this case, the ultimate clinical benefit was progression of renal disease and other significant clinical events. Because reduction of substrate accumulation is not an ICE and is not closely related to the ultimate clinical benefit, FDA needed to exert considerable regulatory scientific scrutiny to carefully observe and understand the Fabry disease process, as well as additionally to understand the relationship between the drug's effect on the surrogate endpoint and the disease. Thus, each of these two FDA-listed factors was given more weight, more significance in the approval of Fabrazyme with its surrogate endpoint than in the approval of Northera with its ICE.

Therefore, if Sponsors and FDA turned to ICE for Accelerated Approvals, the demands on the FDA review process and more importantly, on the FDA approval decisions would be reduced, and it may be that more therapies as a result may be approved.

Proposal #3: Untap the Potential of a Traditional Approval Authority Through Use of a Simple Chart.

PCAST recommended that FDA use more of its existing "traditional" approval authorities. These traditional authorities includes the single study with "confirmatory evidence" statutory standard which was created in 1997, but which has had only limited visibility and even lesser use. One way to achieve both my first proposal (above) and this PCAST recommendation

would be for FDA to adopt a chart that could be used at each FDA Drug Advisory Committee (see Appendix 1). The proposed chart, in an uncomplicated and clear way, would present and made available for consideration all of the FDA's existing approval authorities, along with the 2 major types of therapies for which FDA has historically exercised flexibility.

In 1997, under section 115 of the FDA Modernization Act, or FDAMA, Congress created a new statutory standard of evidence for FDA to use in determining whether a new medicine helps a patient. This evidentiary basis is an alternative to the standard Congress created in 1962, which FDA has usually interpreted as a requirement that two studies each prove a drug benefits a patient statistically, at a level of proof that tells FDA that these results could not have happened by chance more frequently than 1 in 20 times (p value of <.05). The 1997 provision allows FDA to approve drugs based on "one adequate and well-controlled clinical trial with confirmatory evidence."[14] While the third recommendation in the PCAST report was to "expand the use in practice of FDA's existing authorities for confirmatory evidence," by the time the report was published this recommendation no longer addressed the need for implementation of the key phrase of the FDAMA 115 statute: "confirmatory evidence." The need for implementation of the phrase "confirmatory evidence" remains. To date, FDA has not promulgated regulations or provided guidance to industry or FDA reviewers on how to use this approval pathway by defining this key phrase and how to determine when that standard has been met.

For instance, the May 1998 FDA guidance on "Providing Clinical Evidence of Effectiveness" sets out 9 different ways in which a drug may be approved based on a single study;[15] however, in practice, industry, the investment community, academia, and the patient

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[14] Section 115 of Food and Drug Administration Modernization Act of 1997 amending section 505(d) of the Federal Food, Drug, and Cosmetic Act [hereinafter FDAMA 115].

[15] Food and Drug Administration, Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 8-12 (May 1998) [hereinafter May 1998 Guidance].

community, as well as often the FDA too, only recognizes the 9th of these 9 ways set forth by FDA. More importantly, this 9th means of proving effectiveness with a single study in FDA's May 1998 guidance is limited in the extreme. It is only applicable in very limited circumstances. For instance, this specific single study standard from the May 1998 guidance applies generally only when there exists a "statistically very persuasive finding [that is]... a very low p-value"[16] and where to conduct a "second trial would be practically or ethically impossible."[17]

The FDAMA 115 alternative "confirmatory evidence" pathway created by Congress has not found meaningful foothold in the regulatory armamentarium. Only in a handful of occasions has FDA approved drugs with explicit reliance upon this standard. Let me review several of these so that you can see just how different the "confirmatory evidence" was with each case.

In 2004, FDA's Dr. Robert Temple, then Director of the Office of Drug Evaluation 1, approved, under FDAMA 115, the new drug Ventavis. In this case, the confirmatory evidence was the FDA's prior approval of two other "closely related" prostacyclin analogues despite those two other drugs being delivered by injectable means and Ventavis being inhaled.[18] Further, Dr. Temple in that approval of Ventavis, noted that FDA had relied upon evidence of effectiveness from other drugs in the same class to approve new molecular entities. Dr. Temple specifically cited to the approval of Angiotensin II blockers for delaying renal function deterioration in Type 2 diabetes patients and to the approval of ACE inhibitors for treating congestive heart failure in which each approval relied on "single studies with p-values between 0.05 and 0.01 with the backgroup of multiple drugs in the class showing favorable effect."[19]

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16 May 1998 Guidance, 13.

17 *Id.* at 15.

18 Memorandum re Iloprost, NDA 21-779, Cotherix, Inc. from Robert Temple, Director, Office of Drug Evaluation I, CDER, FDA (Dec. 27, 2004) (Appendix 4).

19 *Id.*

In 2008, FDA approved Banzel based on a single trial in patients with a specific seizure disorder, Lennox-Gastaut Syndrome (LGS), with the "confirmatory evidence" coming from 2 trials in a related condition, "partial seizures."[20] The Sponsor had asked for approval for both uses, LGS and partial seizures, and while FDA judged the 2 partial seizure trials to be sufficient as confirmatory evidence of Branzel's anticonvulsant activity to constitute the "confirmatory evidence" of Branzel's benefit in LGS, FDA never approved Banzel for partial seizures. Dr. Temple approved Banzel and Dr. Rusty Katz, then the Director of the FDA Division of Neurology Products, stated at a public meeting that the evidence of effectiveness was established under the single study in LGS with the "confirmatory evidence" from the partial seizure studies, specifically as allowed by FDAMA 115.

FDA approved Xenazine in 2008 for the treatment of Huntington's chorea based on a single trial with robust results on the primary endpoint, and a second trial that did not achieve statistical significance.[21] FDA overlooked the lack of statistical significance in this second study because FDA judged that the estimate of the magnitude of the treatment benefit in the second study was identical to that seen in the single positive study. In the March 2006 "approvable letter," Dr. Temple cited FDAMA 115 as the authority for such an approval.[22]

There is room to build upon the wisdom in the May 1998 guidance so that drug developers, patients, sponsors, and FDA reviewers are aware of all evidence that may establish a product's efficacy. There is the opportunity to better recognize and use the existing FDAMA 115 authority. For instance, I know of a drug in development for a rare disorder that has a Phase

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20 Banzel Summary Review, NDA 21-911, from Russell Katz, Director, Division of Neurology Products, CDER, FDA (Nov. 13, 2008), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021911s000_SumR.pdf.

21 Approvable Letter from Robert Temple, Office Director, Office of Drug Evaluation I, CDER, FDA, to Benjamin Lewis, Senior Director, Regulatory Affairs, Prestwick Pharmaceuticals, In. (Mar. 24, 2006), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021894s000_Approvable.pdf. (Appendix 5).

22 *Id.*

2 study indicating efficacy for treating the hallmark symptom of that disease, with another Phase 2 study in a related condition that report a statistically significant effect in a relevant symptom of that disease. If a single Phase 3 study is conducted in this rare disease population which achieves a p-value of less than 0.05, it may be that the results of the two Phase 2 studies could be sufficient to satisfy the "confirmatory evidence" standard of FDAMA 115.

Where there is scientifically-derived effectiveness information from any of a wide range of relevant sources in a new drug development program, this information should be considered. In the published report from a workshop on FDAMA115 and confirmatory evidence, the key author, Dr. Carl Peck[23]cites Dr. Janet Woodcock who presented the example at the workshop that, if a Sponsor were to seek to obtain FDA approval for an estrogen that was a new chemical entity for the prevention of osteoporosis, the Sponsor would only need to demonstrate improvement in bone mineral density in a single clinical trial.[24] Other substantial evidence supporting the lowest effective dose may still be needed to minimize toxicity, and evidence of dosing could come from the bone density trial or from a phase 2 dose-ranging trial.[25] Most importantly, Dr. Woodcock said that "additional studies would not be required because of extensive scientific understanding and acceptance of estrogen's pharmacological effects on bone mineral density as a surrogate endpoint for osteoporotic fracture rate."[26] In this example, class effects of estrogen on this use would constitute "confirmatory evidence" under FDAMA 115.

Clinical trial designs are no longer marked by nonspecific endpoints, inadequate blinding, unclear rules on analysis, and sketchy protocols. Second, replicate well-controlled trials to rule out unidentified biases in study design are therefore no longer needed in every case. In the case

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[23] Dr. Peck had, at that time, recently been succeeded as Director of the FDA Drug Center by Dr. Woodcock.

[24] Carl Peck & Jill Wechsler, 36 *Drug Information Journal* 517, 526 (2002) [hereinafter Peck Paper] (Appendix 6).

[25] Peck Paper 526.

[26] Peck Paper 526.

of FDAMA 115, Congress has already given FDA the explicit authority, so now Congress could ask FDA to expand its exercise of this authority.

One way for Congress to support more fully FDA's embrace of this evidentiary basis to support a drug's approval, as well as to suggest a way for FDA to give exception to FDA's historic exercise of reasonable flexibility in regulating new inclusions would be for Congress to ask FDA to consider adopting a chart such as the one I am displaying (see Appendix 1) that could be provided to FDA reviewers or members of Advisory Committees to help them visualize the standards for statutory evidence of effectiveness, as well as the two types of therapies which FDA has demonstrated flexibility. As you can see from the first three rows, there generally are three ways to establish "substantial evidence of effectiveness" of a new therapy: (1) two adequate and well-controlled studies,[27] (2) one adequate and well-controlled clinical trial with confirmatory evidence,[28] and (3) a single study of providing highly persuasive and statistical evidence of an important clinical benefit, and where a confirmatory study would be difficult to conduct on practical or ethical grounds.[29] Then, as you can see in the final two rows, there are two classes of therapies for which FDA has historically exercised reasonable flexibility with respect to the quantum and quality of efficacy evidence required for approval: (1) Accelerated Approval Therapies and (2) orphan drugs.[30] The proposed chart, in an uncomplicated and clear way, would present and make available for consideration all of the FDA's existing authorities, along with two major types of therapies for which FDA has historically exercised flexibility.

Proposal #4: Issue a Guidance to Reduce Uncertainty and Communicate an Innovative Advance.

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27 21 U.S.C. § 355(d)(7).

28 FDAMA 115.

29 May 1998 Guidance at pp 12-16.

30 *See* Frank Sasinowski, *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloging FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders*, 46 Drug Information Journal 238 (Mar. 2012) (Appendix 7).

PCAST recommended that FDA increase its use of Guidances and White Papers to communicate innovative advances in regulatory science.[31] FDA could be encouraged to issue a Guidance on the use of cumulative distribution analyses of clinical trial results as one way to aid in assessing the clinical meaningfulness of a therapy. FDA has been increasingly employing this type of analysis, and issuing an FDA Guidance or White Paper would give this type of analysis a broader and formal FDA endorsement, and this Guidance then would benefit drug development by clarifying the drug development pathway and by reducing regulatory uncertainty.

FDA ought to be and has been appropriately sensitive to refraining from imposing new regulatory requirements that are not explicitly in the statute. With respect to "clinical meaningfulness," the statute requires sponsors to establish evidence that "the drug will have the effect it purports."[32]

The first time I heard an FDA official question whether a statistically significant study finding was also "clinically meaningful" to a patient was Dr. Robert Temple at an April 2006 advisory committee for a treatment of pain from anal fissures.[33] In the study of this therapy, pain was reported on a 100mm visual analog scale (VAS), and the drug-treated arm of the study showed a 29-point improvement from baseline, while subjects on placebo reported a 26-point improvement. There was some discussion during the committee's proceedings about whether this numerical difference was a statistically significant difference. Dr. Temple instead conceded as a "thought-exercise" that this numerical difference was not due to chance but was caused by the drug, and then Dr. Temple asked, however, whether a patient suffering from anal fissure pain could tell the difference between a 29-point and a 26-point improvement between the average

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31 PCAST Report at pp. 42-48 and PCAST Recommendation #1 at p. 54, item (iii).
32 FDC Act § 505(d).
33 April 26, 2006 Advisory Committee on Cillegesie (nitroglycerin ointment).

patient's baseline pain score and that patient's pain scored at final visit. This was my introduction to the concept of "clinical meaningfulness," and FDA seemed to be articulating a very reasonable question. However, since that day long ago, some at FDA have taken the concept and challenged sponsors to establish by empirical evidence the "minimally clinically important difference" (MCID) for a study's endpoint prior to beginning the sponsor's pivotal clinical trial or trials. Not only does this impose a tremendous burden in terms of both time and resources which discourages and impedes innovation, but its utility is of uncertain value and may even be overtly misleading. Said more plainly, requiring this may not only deter and definitively delay development, but that deterrence and delay may be a price paid for achieving an MCID that may be of negative value.

In addition, any requirement to establish an MCID *a priori* and then analyze the results by only assessing "responders" generates waste in clinical trials, for we are then essentially ignoring all the subjects that happen to "fall short" of the MCID cut-point. More importantly, these MCID cut-points do not account for the heterogeneity in how each individual may differently assess "clinical meaningfulness" for that subject. In other words, these MCID cut-points are actually artificial, or population-derived values, that may not be relevant to individual patients. To understand this, consider the following example of FDA's February 2014 approval of Northera for orthostatic hypotension (OH). The key life-altering symptom for patients with OH is dizziness. When studying the effect of the drug Northera on dizziness, an MCID cut-point could have been established such that only those patients that reported an improvement of at least one point on the 11-point dizziness scale would be considered responders.[34] By doing so, all of the results on those subjects who reported an improvement of less than one point would be

[34] Northera (droxidopa) Label (2014), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203202lbl.pdf.

thrown out of the analysis, and ignoring study results is not sound statistically. In addition, for any subject, a 1-point improvement or above may not be the right definition for that person of "clinically meaningfulness." Consider the hypothetical cases of a ballet dancer and a lawyer: two tenths of a one-point improvement might be meaningful to a ballet dancer if even that small amount of improvement enables that person to continue to dance, while conversely a lawyer with OH who primarily sits in front of a computer all day may need a two-point improvement for that to be of sufficient magnitude for it be a clinically meaningful difference to that person.

In addition, when a drug company is required to select an MCID before conducting a trial, they are burdened with doing preliminary work to select the cut-point. They then also need larger and/or longer trials to detect a difference between drug and placebo/control arms in the study because the MCID responder analysis statistically is less sensitive to detecting between-group differences than a continuous variable.

As an alternative to MCID, FDA has been employing a "cumulative distribution" analysis of results, where a wide swath of different cut-points are analyzed. Cumulative distribution will improve interpretation of clinical trial data, as they show the full pattern of response using all subjects and results, and therefore, this type of analysis enables the entire distribution of responses to be compared between study groups. This is not a new concept for FDA for FDA has pioneered it and has reported such analysis in the labeling of several approved therapies. See below for excerpts from the labeling of the February 2014 approval of Northera for neurogenic orthostatic hypotension and the October 2013 approval of Adempas for pulmonary hypotension.

Table 1 - Northera Cumulative Distribution Curve

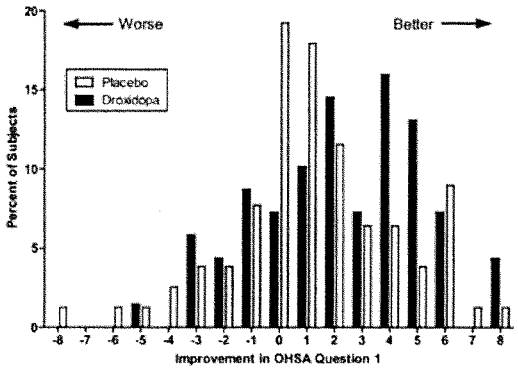
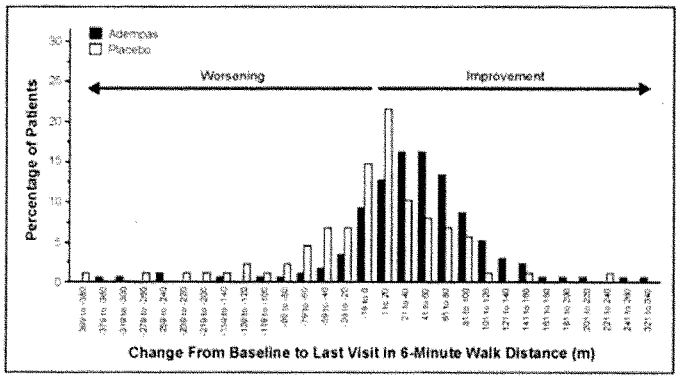


Table 2 - Adempas Cumulative Distribution Curve



Conclusions

1. My analysis of FDA's use of Accelerated Approval authority shows that FDA knows how to use this authority and indeed, how to use it flexibly. Therefore, to embrace the mutual recommendations of PCAST and FDASIA to employ this approval authority more will not require FDA to break new ground but to continue by expanding more what it has already done.

My first proposal is that this could be accomplished by adopting a practice of considering its Accelerated Approval authority for each new therapy.

2. Congress could recognize the historic flexibility FDA has exercised in its Accelerated Approvals (as well as in approving orphan drugs) and encourage further flexibility. Accelerated approval is not a rigid regime. It is necessarily flexible, and FDA has demonstrated its ability to act on therapies flexibly. To expand this flexibility, my second proposal is that Congress urge the increased acceptance and use of intermediate clinical endpoints (ICE).

3. Congress could also encourage FDA to expand the use in practice of its existing authorities for single-study approvals with confirmatory evidence under FDAMA 115, as was originally intended by Recommendation #3 in the PCAST report. As to my third proposal, as Appendix 1, I direct your attention to the chart, which is included in this written testimony, as a model for informing FDA reviewers, patients, sponsors, and Advisory Committee members about the options drug developers have to demonstrate a therapy's effectiveness, as well as to emphasize the two principle routes to FDA's historic exercise of flexibility in the case of both Accelerated Approval therapies and orphan drugs.

4. My fourth proposal is that Congress consider encouraging FDA to issue a Guidance on the emerging concept of "cumulative distribution" as a means of showing a therapy's clinical meaningfulness.

In these 4 ways, Congress could encourage the development and approval of treatments for serious and life-threatening diseases.

* * * * *

I thank you again for the invitation to participate in this hearing and hope these comments are valuable as you move forward with the 21st Century Cures initiative, and the Committee's work to accelerate the development of promising new treatments for patients.

Frank Sasinowski's May 20, 2014 Testimony Before House E&C Health Subcommittee

On behalf of his law firm, Hyman, Phelps & McNamara, P.C., and as a Director of the National Organization for Rare Disorders (NORD), Frank Sasinowski offered the following.

1. Increase Accelerated Approval's Visibility and Use by Considering it for Each New Therapy.

Both PCAST and FDASIA recommended that FDA expand, beyond cancer and AIDS, use of its Accelerated Approval authority to approve medicines for those with serious diseases and no available therapies. Mr. Sasinowski's September 2013 analysis of the 19 therapies approved since 1992 (when FDA created Subpart H) shows that FDA has already been exercising considerable, reasonable flexibility in using this approval authority. This means that to implement the PCAST and FDASIA recommendation to use this authority more often, FDA would not need to establish any new program or policies, but may only need to give this approval pathway more visibility and more frequent consideration. Congress could encourage FDA to adopt a practice of considering whether each therapy may be eligible for Accelerated Approval This simple change would require nearly no resources or time, but could have a huge impact on Americans' access to medicines for serious diseases. Also, see Proposal #3 below.

2. Using ICE More May Increase the Number of Accelerated Approval Therapies.

PCAST recommended that FDA consider using Intermediate Clinical Endpoints (ICE) more often for Accelerated Approvals. Mr. Sasinowski's analysis (see above) was based on the 3 major factors in FDA's June 2013 Draft Guidance. Mr. Sasinowski concludes that 2 of these 3 major factors would be significantly reduced in the FDA's review process if FDA and sponsors shifted to use ICE instead of unvalidated surrogates. Therefore, Mr. Sasinowski proposes that using ICE more would, according to his analysis, help FDA by reducing the demands of FDA's review of therapies under Accelerated Approval, which may yield greater numbers of therapies approved by this pathway.

3. Untap the Potential of a Traditional Approval Authority through Use of a Simple Chart.

PCAST recommended that FDA use more of its existing "traditional" approval authorities. These traditional authorities includes the single study with "confirmatory evidence" statutory standard which was created in 1997, but which has had only limited visibility and even lesser use. One way to achieve both Mr. Sasinowski's first proposal (above) and this PCAST recommendation would be for FDA to adopt a chart that Mr. Sasinowski proposes be used at each FDA Drug Advisory Committee (attached). The proposed chart, in an uncomplicated & clear way would present and made available for consideration all of the FDA's existing approval authorities, along with the 2 major types of therapies for which FDA has historically exercised flexibility.

4. Issue a Guidance to Reduce Uncertainty & Communicate an Innovative Advance.

PCAST recommended that FDA increase its use of Guidances and White Papers to communicate innovative advances in regulatory science. Mr. Sasinowski proposes that FDA issue a guidance on the use of cumulative distribution analyses of clinical trial results as one way to aid in assessing the clinical meaningfulness of a therapy. FDA has been increasingly employing this type of analysis, and issuing an FDA Guidance or White Paper would give this type of analysis a broader and formal FDA endorsement, and this guidance then would benefit drug development by reducing regulatory uncertainty.

[Supporting documents submitted by Mr. Sasinowski are available at http://docs.house.gov/Committee/Calendar/ByEvent.aspx?EventID=102237.]

Mr. PITTS. The Chair thanks the gentleman.

Now recognize Mr. Allen, 5 minutes for an opening statement.

STATEMENT OF JEFF ALLEN

Mr. ALLEN. Good morning, Chairman Pitts, Ranking Member Pallone, and members of the subcommittee.

I am Jeff Allen, Executive Director of Friends of Cancer Research, a think-tank and advocacy organization dedicated to accelerating science and technology from bench to bedside.

It is an honor to be here, and I would also like to thank our founder and driving force, Ellen Sigal, who is here today as well.

Today, I would like to focus on a few of the key items identified within the report to the President, by describing areas in which there has been significant progress, and areas to which the committee might turn its attention and resources.

One key challenge that the working group explored was improving drug regulation at FDA. The authority and tools to fill FDA's monumental responsibility continues to evolve to keep pace with current science. I would like to provide a few examples that demonstrate this.

In collaboration with our expert colleagues from FDA, NIH, patient advocacy industry, and academia, we at Friends of Cancer Research proposed a series of approaches of how clinical testing could be modified to expedite the development of new targeted therapies that show dramatic clinical activity early in development. With the leadership of this committee, and your colleagues in the Senate, the creation of the new FDA program called the Breakthrough Therapies Designation was codified into law as part of the FDA Safety and Innovation Act.

FDA has been rapidly implementing the program in many serious disease settings, and, Mr. Chairman, I am happy to report that in just 2 years, 178 requests for breakthrough designation have been submitted, 44 have been granted, and 6 breakthrough therapies have been approved.

It has been estimated by some of the sponsors of the drugs that the breakthrough therapy program accelerated the development process by several years, without compromising the long-held standards for safety and efficacy. The all-hands-on-deck approach demonstrates the importance of the public-private collaboration that the designation brings to enhanced science-based regulation, translating to reduced development times, increased investment in the biotech sector, and the improved health of patients that previously had few treatment options. This is an incredible example of Congress putting partisan politics aside, and acting deliberately to address one of our country's most pressing health issues.

Another key component of the report to the President explored ways of addressing inefficiencies in clinical trial conduct. There is no doubt that our antiquated patchwork clinical trial system makes developing new treatments a cumbersome, expensive and protracted process.

To being to address this issue directly, and truly change the course of how trials are done, Friends of Cancer Research is spearheading a project working with a large diverse set of partners from academia, industry, Government and advocacy, to develop a modern-day clinical trial as innovative as the therapies it seeks to test. In this project, called Lung Map, a master protocol will govern how multiple drugs, each targeting a different biomarker, will be tested as a potential treatment for lung cancer. Each arm of the study will test a different drug, and utilize cutting-edge screening technology to identify which patient is a molecular match to each arm. This will create a rapidly evolving infrastructure that can simultaneously examine the safety and efficacy of multiple new drugs. Lung Map has the ability to reinvigorate the research enterprise, and rapidly facilitate the development of molecularly targeted medicine. This approach has the ability to improve enrollment, enhance consistency, increase efficiency, reduce cost, and most importantly, improve patient lives.

One way that the FDA communicates to researchers and developers about new approaches or changes to current policy is through guidance documents, an interchange that is vital to modernizing the enterprise. The report recommends that external partnerships could be beneficial in providing input on scientific subjects that would be fit for guidance. Neutral public venues that can facilitate the exchange of ideas can greatly inform the topics and approaches that FDA may take when considering best practices and guidance development. Much like FDA benefits from hearing the challenges faced by the research community, the external community gains from hearing from FDA. Processes and adequate funding levels need to be established to increase FDA's ability to gain external input and develop new guidance. This has the ability to greatly enhance the success of research endeavors, encourage innovation—innovative collaborations, and can inform by the legislation.

In addition to the elements raised in the report, we at Friends of Cancer Research believe that consideration should also be given to opportunities in the development of companion diagnostics. Building on the foundation that FDA has provided through recent guidance, this committee could facilitate new policies to advance how novel technologies can inform the use of new drugs to ensure that the right patients have access to the right treatments at the right time.

The examples that I have provided today are case studies that can be learned from, and are steppingstones upon which more work can be done. Innovation is incremental, but with better understanding of the disease processes, these incremental steps toward improving health can and will be transformational. The regulatory framework has been put into place, and enhanced collaborations will be needed to uncover new breakthroughs and alleviate inefficiencies. Aligning policies with the current state of science can enhance biomedical research and improve the lives of patients. The 21st Center Cures Initiative can be the next step toward that goal.

[The prepared statement of Mr. Allen follows:]

21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation

Testimony Before
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

Jeff Allen, PhD
Executive Director
Friends of Cancer Research

May 20, 2014

21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation

Testimony of Jeff Allen, PhD, Executive Director, Friends of Cancer Research

Good morning, Chairman Upton, Ranking Member Waxman, Subcommittee Chairman Pitts, Ranking Member Pallone, and Members of the sub-committee. I am Dr. Jeff Allen, Executive Director of Friends of Cancer Research, a cancer research think tank and advocacy organization dedicated to accelerating science & technology from bench to bedside. I would like to thank all Members and the staff of this committee for putting together this important hearing. It is an honor to testify before you today and provide our perspective as you embark on this important 21st Century Cures initiative, and I'd like to especially thank Chairman Upton and Congresswoman DeGette for undertaking this endeavor. Along with my colleagues here, I also had the pleasure of serving on the working group that contributed to the September 2012 ***Report to the President of the United States on Propelling Innovation in Drug Discovery, Development and Evaluation.***

While compelling progress has been made within the field of oncology, there is much more to be done to alleviate the current cancer epidemic and profound suffering it causes. It is estimated that, in 2014, over 1.66 million Americans will be newly diagnosed with cancer. If something is not done, cancer will claim the lives of 585,720 mothers, fathers, grandparents, sisters, brothers, and friends, this year.[1] This, Mr. Chairman, is roughly the equivalent of every citizen in your home county of Lancaster, Pennsylvania. This profound human toll also comes with a staggering cost to our health care system of an additional $226 billion dollars.[2,3]

[1] The American Cancer Society Facts & Figures: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf Accessed 5/19/14

[2] The American Cancer Society: http://www.cancer.org/Cancer/CancerBasics/economic-impact-of-cancer Accessed 5/19/14

Improved ways to combat cancer are urgently needed. Advancements in basic science have never been more profound, but unfortunately they do not always translate into new treatment as rapidly as patients deserve. Recent estimates indicate that it currently could take upwards of 12 years and over $1 billion to develop a new cancer drug.[4] With all of this personal and economic loss, and the hurdles new therapies face, there is still great hope and resilience by patients and there is incredible work being done across all sectors to battle this and many other life-threatening diseases. The remarkable advancements being made at the National Institutes of Health (NIH), at academic medical centers all across the country and within private sector industry is rapidly changing how we look at disease, and how we are able to treat patients. The drugs and biologics being developed today to treat many different diseases are far more effective, but also more complex than their predecessors. I, and millions of people across this country, hope that the work of this committee will be a catalyst to accelerate getting the right medicines to the right patients at the right time.

Much like this Committee is examining the current state of developing new medicines though 21st Century Cures, the Working Group that developed the report to the President was charged to identify key barriers to optimal new drug development and make recommendations on how they might be addressed. I would like to focus on a few of the key areas identified within the report, describing both areas in which there has been significant progress and areas to which the committee might turn its attention and resources to further enhance.

Improving Drug Regulation – Breakthrough Therapy Designation

One key challenge that the working group explored was *Improving Drug Regulation.* The role of the FDA is to protect and promote the health of the American public by ensuring the safety, effectiveness,

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[3] http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041782.pdf Accessed 5/19/14

[4] Adams, C. P. and Brantner, V. V. Health Economics, 19 (2010), 130–141. doi: 10.1002/hec.1454

and security of medical products, devices, food, and cosmetics.[5] The authority and tools to fulfill this monumental responsibility continues to evolve to keep pace with the current state of science. I'd like to provide you with a few examples that demonstrate this.

With the expansion of knowledge about the biological basis of complex disease, new therapies are being developed that are targeted to unique molecular changes known to "drive" a disease. These new, "targeted therapies" allow selection of patients highly likely to respond to the new treatment. For these new treatments (or combinations) that show the promise of dramatic clinical activity and significant improvement over currently-available treatment early in the new drug's development, the traditional multi-phase, sequential development approach is not be appropriate, particularly if existing treatment options have limited efficacy.

In collaboration with our expert colleagues from FDA, NIH, patient advocacy, industry, and academia, we at Friends of Cancer Research proposed a series of approaches of how clinical testing could be modified to expedite the development of these new "breakthrough therapies." With the leadership of this committee, and your colleagues in the Senate, the creation of a new FDA program called the "Breakthrough Therapies Designation" was codified into law as part of the Food and Drug Administration Safety and Innovation Act (FDASIA).[6]

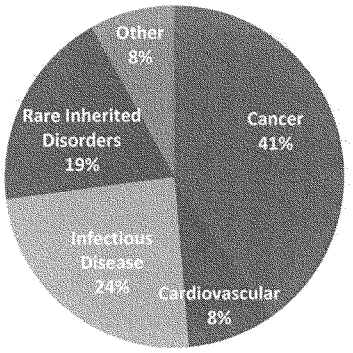
FDA has rapidly implemented this new regulatory tool. It is important to note that the Breakthrough designation preserves the standards of safety and efficacy that have been in place for over 50 years, but when a new drug shows such and unprecedented effect, like current science is allowing, a new approach is needed. [7] Once a breakthrough therapy designation is granted, different divisions of FDA and the drug sponsor begin an intensive collaboration to plan the future research with the drug. Through this

[5] About FDA: http://www.fda.gov/AboutFDA/Transparency/Basics/ucm192695.htm Accessed 5/16/14
[6] FDASIA Sec. 902 Breakthrough Therapies. Public Law 112-144
[7] Kefauver-Harris amendments to the 1938 Food, Drug, and Cosmetic (FD&C) Act [PL 87-781; 76 Stat. 788-89]

collaboration an expedited, and optimally efficient, development program of the Breakthrough drug is designed and executed.

Mr. Chairman, I am happy to report that in just two years, 178 requests for Breakthrough Designation have been submitted, and 44 designations have been granted.[8] While the basis for developing this new tool may have utilized cancer as a case study, it was not envisioned that this program should be applied only to cancer drugs, and as shown below, FDA has been rapidly implementing the program in many serious disease settings.

Breakthrough Therapy Designations by Therapeutic Category



Since its passage into law, there have been 6 breakthrough therapies that have successfully completed testing and are now FDA approved drugs. It has been estimated by some of the sponsors of the drugs that the Breakthrough Therapy program accelerated the development process by several years. The "all hands on deck" approach demonstrates the importance of the public-private collaboration that the

[8] FDA CDER and CBER Breakthrough Requests: http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm341027.htm Accessed 5/16/14

Breakthrough designation brings to enhancing science-based regulation; translating to reduced development times, increased investment in the biotech sector, and improve the health of the patients that previously had few treatment options. This designation and the process to create it is an incredible example of congress putting partisan politics aside and acting deliberately to address one of our country's most pressing health issues. For that, I want thank this Committee and the Congress for enacting this new law.

Improving Drug Discovery and Development – Lung-MAP

Another key component of the report to the President explored ways of addressing inefficiencies in clinical trial conduct. The report describes clinical trials as, "the largest single component of the R&D budget of the biopharmaceutical industry, at approximately $31.3, representing nearly 40 percent of the R&D budget of major companies."[9] There is no doubt that our antiquated, patch-work clinical trial system makes developing new treatments a cumbersome, expensive and protracted process. In order to truly realize the promise of evolving science, new models and tools, ones that capitalize on the rapid scientific discovery including modern informatics, are needed. However, innovative paradigms to evaluate potentially promising drugs will only be successful through multi-sector collaboration.

To begin to address this issue directly, and truly change the course of how trials are done, Friends of Cancer Research is spearheading a project which in many ways originated at the FDA itself. We are currently working with a large, diverse set of partners from academia, industry, government and advocacy to develop a modern day clinical trial as innovative as the therapies it seeks to test. In this project, called Lung-MAP, a "master" protocol will govern how multiple drugs, each targeting a different biomarker, will be tested as potential treatments for lung cancer. Each arm of the study will test a different drug that has been determined to target a unique genetic alteration. The use of cutting-edge

[9] Report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation. Sept 2012; p.20

screening technology will help identify which patient is a molecular match to each arm. This will create a rapidly evolving infrastructure that can simultaneously examine the safety and efficacy of multiple new drugs. This approach will have the ability to improve enrollment, enhance consistency, increase efficiency, reduce costs, and most importantly - improve patients' lives.

Much like advancements in regulation should be driven by cutting-edge science, so too should be the approach to designing new research paradigms. Lung-MAP has the ability to reinvigorate the research enterprise and rapidly facilitate the development of molecularly targeted medicine. It is our hope that this can serve as a template for the future of clinical research. As the project moves forward, each of our partners has committed to do business differently. Mr. Chairman, this project has begun to change culture. We have five of the largest pharmaceutical companies working together, and willing to do what it takes to make sure patients have therapies available that can improve and save lives. This is crucial - the patients that we are striving to help simply do not have time to wait.

There are other public-private efforts that strive to enhance different components of the biomedical research enterprise. For example, the Foundation for the NIH (FNIH) supports the scientific mission of the NIH by uniting experts and resources around specific projects identified by the Institutes' directors. In addition to playing a critical role in Lung-MAP, the FNIH supports project ranging from biomarker discovery, advancement of Alzheimer's research, improvement of global health and NIV/AIDS vaccine discovery. Similarly, the Reagan-Udall Foundation was established by the Congress in 2007 to facilitate research in support of the mission of the FDA and the advancement of regulatory science. Their work includes the Observation Medical Outcomes Partnership to support drug safety research methodology, efforts to develop tuberculosis treatment regimens, and improve understanding of the mechanisms of toxicology. Other specific efforts include the Clinical Trial Transformation Initiative, whose specific mission is to identify and promote practices that will increase the quality and efficiency of clinical trials.

Each of these initiatives, and many others, represent public-private efforts to enhance medical research at different points along the continuum. The report to the President also acknowledged their potential. With appropriate resources, these on-going collaborations have the ability to help address the challenges to discovering and developing new medicine and ultimately improve human health.

Improving Scientific Communication – Guidance Development

One way that the FDA communicates to researchers and developers about new approaches or changes to current policies is through the use of Guidance Documents. These documents provide FDA's view on current challenges, provide clarity and often times recommendations to industry and prompting vibrant discussion and debate among those involved in drug development – an interchange that is vital to modernizing the enterprise.

These documents communicate best practices internally within FDA as well as to external stakeholders. However, developing them is resource intensive. Given the breadth and continuously growing responsibilities of FDA staff, contributing to a scientific activity such as the development of a Guidance document often becomes secondary to their primary job. Critical activities such as providing scientific communication to external stakeholders is just one of the many functions of FDA that can suffer as a result of insufficient resources. The duties of the agency is often increased without matching appropriated dollars in tandem, and user fees are infrequently able to be applied to the many Guidance documents that FDA works to develop. This is one of many specific examples of how additional resources could benefit the FDA it its mission to help patients.

The report, and the working group's deliberations, did include the importance of new FDA Guidance documents. The report suggested that external partnerships could be beneficial in providing input on

scientific subjects that would be fit for FDA Guidance. [10] FDA is often constrained on how they can receive input from external stakeholders, but scientific exchange between all stakeholders involved in biomedical research is critical to its success. Neutral, public venues that can facilitate the exchange of ideas can greatly inform the topics and approaches that FDA may take when considering best practices and guidance development. Without such preliminary discussions, and input from thought leaders in the field of science and medicine, the agency is left to develop Guidance documents and only receive public input once they are complete as part of the routine comment period.

We have seen the benefits of early interactions firsthand, and have developed a model to bolster the access to expertise that the FDA has as they deliberate guidance. Noting the promise that combinations of new drugs have shown to combat diseases like HIV and cancer, we convened an expert group to provide specific ideas on how novel combinations could optimally be developed. FDA was part of that working group and was open and wiling to be a part of these expert discussions and recommendations. The FDA completed their own internal process to develop guidance on this topic but the rapidity with which the guidance was released suggests that the broad, thoughtful scientific discussion, of which FDA was privy, appears to have accelerated the process.

The same is true with the development of important Guidance documents issued last year regarding the development of companion diagnostics to support drug development[11] and the recently issued draft guidance proposing a program for expedited access to medical devices to treat serious diseases.[12]

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[10] Report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation. Sept 2012; p.55

[11] Co-Development of Two or More Investigational Drugs for Use in Combination: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf June 2013. Accessed 5/16/14

[12] Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf. April 2014. Accessed 5/16/14

Much like FDA policies benefit from hearing the challenges faced by the research community, the external community gains from hearing from FDA. Processes and funding streams need to be established to increase FDA's ability to gain external input and develop new Guidance documents. Guidance documents like these and many others have the ability to greatly enhance the success of research endeavors and encourage the types of innovative collaborations like Lung-MAP and can inform vital legislation like Breakthrough.

Improving Drug Discovery and Development – Companion Diagnostics

The PCAST report was specifically focused on propelling new drug development, and while the working group focused their deliberations on this specific topic, I believe that considerations should also be given to opportunities in the development of companion diagnostics. In the prior examples of successful, science-based initiatives in research and regulation, Lung-MAP is based on advanced screening technology that can detect different genetic alterations for which a drug may target. For Breakthrough Therapies, over half of the currently designated drugs utilize some sort of tool to identify the subset of patients most likely to benefit from the drug.

The use of a companion diagnostic to guide the use of new therapies has become increasingly important. The FDA recently took proactive steps to issue important Guidance documents last year regarding the development of companion diagnostics to support drug development[13] and recently issued draft guidance proposing a program for expedited access to medical devices to treat serious diseases.[14] These Guidance documents provide new pathways and important advice to the research

[13] Co-Development of Two or More Investigational Drugs for Use in Combination: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf June 2013. Accessed 5/16/14

[14] Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf. April 2014. Accessed 5/16/14

community. Building on the foundation that FDA has provided, this Committee could facilitate new policies to advancement of how novel technologies can inform the use of new drugs to ensure that the right patients have access to the right treatments at the right time.

Conclusion

The state of science and medicine has never been as promising as it is today. The 21st Century Cures initiative is an important way of examining new policies to ensure that new discoveries are rapidly translated to life improving treatments for patients. The examples that I have provided today are case studies that can be learned from, and are stepping stones upon which more work can be done. Innovation is incremental, but with continually improved understanding of disease processes, these incremental steps toward improving health can and will be transformational. This, however, is only made possible with adequate support, including increased funding, for critical health agencies like NIH and FDA. The regulatory framework has been put into place to accelerate the development of medical breakthroughs. Enhanced collaborations, like Lung-MAP, will be needed to uncover such breakthrough and alleviate current inefficiencies. Aligning policies with the current state of science has the ability to accelerate the development of safe and effective therapies to improve the state of biomedical research and improve the lives of patients. The 21st Century Cures initiative can be the next step toward that goal.

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About Friends of Cancer Research

Friends of Cancer Research is our country's leading voice in advocating for policies and solutions that will get treatments to patients in the safest and quickest way possible. Friends of Cancer Research (Friends) develops groundbreaking partnerships and creates a more open dialogue among both public and private sectors and tears down the barriers that stand in the way of conquering cancer. By collaborating with premier academic research centers, professional societies, and other advocacy organizations, Friends is able to accelerate innovation. www.focr.org

For more information please contact: Ryan Hohman, JD, Managing Director, Policy & Public Affairs, Friends of Cancer Research at rhohman@focr.org or 202.944.6708

Mr. PITTS. The Chair thanks the gentleman.

Now recognizes Dr. Tunis, 5 minutes for an opening statement.

STATEMENT OF SEAN R. TUNIS

Mr. TUNIS. Well, I would also like to thank Chairman Pitts, Mr. Pallone, and the members of the subcommittee for the chance to testify today.

Again, my name is Sean Tunis, and I am currently the CEO for the Center for Medical Technology Policy. It is a nonprofit that works on bringing together stakeholders to improve the quality and efficiency of clinical research.

I did serve as one of the invited experts to the PCAST council members and staff, and because of my former role as chief medical officer for the Medicare Program, I thought it would be most useful to reflect on these recommendations in the report from the perspective of the payer and the health system. It wasn't directly addressed in the report, but a number of the recommendations have implications for the health delivery system that I think need to be thought through more carefully in order to ensure that the recommendations can be implemented successful.

And I really think the—kind of the key message I wanted to deliver and what it comes down to is that because many of the recommendations in the report essentially shift evidence requirements and data development from the pre-market space to the post-market space, in other words, the delivery system, it is going to be important to think about how it is going to be possible to efficiently conduct clinical research in the post-market environment, in other words, how do we embed the evidence development that is not generated preapproval in the context of delivering clinical care. And so I am going to offer 3 recommendations or suggestions about how that kind of evidence can be produced.

Just to briefly highlight the recommendations in the PCAST report that sort of have this effect, essentially, of shifting clinical research and evidence development to the post-market space, of course, there is the increased use of accelerated approval, depends more on intermediate and surrogate markers, and, therefore, the expectation is that more of the evidence of safety, effectiveness and even value are going to be generated while these products are in use in the delivery system. The special medical use as well as the adaptive licensing mechanisms also have the same effect, which is, again, to require the ability to do efficient clinical research and data collection in the post-market space.

So in order for the PCAST recommendations, I think, to have the desired impact, which is to speed innovation, and to do that in a way that doesn't in some way compromise the expectation of safe, effective and high-value medications in clinical use, we are going to need, again, to think about how do we get that kind of data out of the delivery system.

As members of the subcommittee know very well, what is simultaneously going on to these innovation discussions is a lot of health systems reform that is increasingly pushing payers and the health systems to be looking for improved effectiveness, real-world effectiveness, and even the value of new medications. So at the same time as we are hoping to introduce new drugs into the healthcare

system with less information about safety and efficacy, we are also putting pressure on payers and providers and health systems to demand more evidence of comparative effectiveness and value in order to be able to deliver high quality and efficient care. So we have got some tension between what we are trying to do on each ends of this policy spectrum.

So, again, I think the solution to this is to think about ways in which we can be more efficient about data development in post-market studies. And basically, I will mention three kinds of components that I think are important to this. The first one is developing more clarity about what constitutes adequate evidence of effectiveness and value from the perspective of payers, clinicians and patients. And what I really mean by this is, in the same way that regulators produce guidance to explain what kinds of studies are necessary to achieve regulatory approval, there is currently nothing that provides guidance to product developers on what meets expectations of real-world effectiveness and value. And so, in a sense, the whole world of regulatory science, which is all about giving product developers clear guidance on clinical development, I think needs to be kind of mirrored in something you might call reimbursement science, which is how do you develop evidence for reimbursement decisions.

The second recommendation is, and some people might think reimbursement science is an oxymoron, but, you know, possibly we will make some progress.

The second and third recommendation, since I am running out of time, is—one is that we need to build infrastructure in the healthcare system to do better research. The NIH is working on that. And, finally, we are going to need to find reimbursement mechanisms that are actually conditional on collecting additional data. Medicare has used coverage with evidence development. There are other forms, but if we are actually going to be shifting these data collection requirements to post-approval, we need the payers to be willing to pay for things while they are being evaluated, much like the FDA has post-approval authority. I think the payers need to implement post-reimbursement authorities for—to collect the additional data on safety and effectiveness.

So thanks again for the opportunity to testify.

[The prepared statement of Mr. Tunis follows:]

Hearing on "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation"

Committee on Energy and Commerce
Subcommittee on Health
United States House of Representative

Testimony of:

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May 20, 2014

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Introduction

Chairman Pitts, Vice-Chairman Burgess, Representative Pallone, and members of the committee - thank you for the invitation to appear before this committee today. As you are aware, the PCAST report on Innovation in Drug Development contains a number of thoughtful, well-crafted and potentially impactful recommendations for more rapidly translating decades of basic science discoveries into new therapies for high priority health needs. In addition to the important public health benefits of innovation, there are tremendous potential economic benefits to promoting the health of the life sciences industry, further highlighting the importance of the work that PCAST has done.

I served as one of the invited experts that worked with the PCAST Council members and staff in developing this report. Because of my former role as chief medical officer at the Centers for Medicare & Medicaid services, my input during working meetings and draft reviews generally reflected a payer/health system perspective. Throughout the discussions, it was clear that the main focus of the report was on innovation and clinical development activities that took place prior to or during regulatory review. For that reason, I thought it would be most useful for this hearing to reflect on the report's recommendations from the vantage point of "post-regulatory decision makers", including public and private payers, health delivery systems, providers, clinicians and patients. It is clear to most innovators and investors that reimbursement and other post-regulatory market dynamics are increasing significant with respect to the early stages of innovation in drug development. The goal of this testimony is to explore the implications of the PCAST recommendations in this broader context.

Of the various "post-regulatory decision makers" listed above, my focus will be mostly on the impact of payer and health systems decision making on innovation in drug development, followed by several recommendations related to these groups that could help to facilitate successful implementation of the recommendations in the PCAST report.

PCAST recommendations on improving drug evaluation

Several of the key recommendations in the PCAST report (recommendations 3,4, and 5) focus on policy mechanism to speed up the evaluation of new drugs. These include the proposal to expand use of FDA's

existing authorities for accelerated approval, a directive that was also reinforced in the FDA Safety and Innovation Act of 2012. Under accelerated approval, the FDA may approve products based on their impact on a surrogate or intermediate endpoint (such as a laboratory test result) that is reasonably likely to predict clinical benefit (outcomes that patients experience directly). Another mechanism recommended to speed the approval of important new drugs is the proposal to approve new drugs more quickly by identifying specific patient subgroups for which the benefit-risk balance is particularly favorable. Use of the drug in these patients is referred to as a "special medical use". Surrogate or intermediate outcomes may also be adequate for approval in this context. The patient subgroups targeted in this approach are those with serious manifestations of a disease, or at high risk of developing severe disease. Finally, the report suggests that the FDA conduct pilots of new "adaptive approval pathways" which would also provide a mechanism for new drugs to be approved in iteratively expanded patient populations as additional evidence from clinical studies is collected. As with special medical use, the intent of this mechanism is to speed the approval of drugs for patients with severe disease by focusing initially on patient subgroups expected to experience the greatest benefit.

Taken together, these recommendations have the potential to considerably reduce the time and expense required to complete pre-market trials and obtain regulatory approval for pharmaceutical and biotech products targeted to important unmet health needs. They also create a new challenge from the perspective of payers, health systems and other post-regulatory decision makers. Clinical and policy decisions on coverage and payment of new drugs have generally assumed that pre-approval studies have demonstrated with a fairly high level of confidence that the drug offers a net improvement in clinical outcomes (not intermediate outcomes). Furthermore, the historically high evidentiary bar for regulatory approval has offered some level of reassurance that some degree of off-label use may benefit patients without exposing them to significant or unknown risks.

It is unclear at this point, and was not discussed in detail in the PCAST deliberations, how the payers, health systems and other post-regulatory decision makers might react to the proposed mechanisms for more rapid regulatory approval. In order for this group of recommendations to have the desired impact on innovation, as well as patient benefit, it is important to develop a clear understanding of this post-regulatory landscape of decision makers, most importantly the health plans and delivery systems. There is no point in creating a regulatory superhighway for innovation that ends in White Oak (FDA) that simply turns into a reimbursement gravel road all the way from there to Security Blvd (CMS).

Payers, Health Delivery Systems and Innovation

As a result of health spending trends and resulting payment reforms, health systems, payers and providers are under increasing pressure to improve health care outcomes while lowering overall health care costs. Most health care policy discussions emphasize the urgency of maximizing value and efficiency of care, and this has inevitably become an increasing consdiration in coverage and payment decisions regarding new drugs, devices, procedures, diagnostics and all other health technologies.

Increasingly, what payers and health systems are looking for with respect to drugs and other technologies is a high level of confidence that the technology will produce meaningful improvements in health outcomes that matter to patients, and at a reasonable incremental cost. Even more desirable would be new products that produce greater clinical benefit with a net reduction in health care spending. Many post-regulatory decision makers recognize the value of innovation, but given the increasing pressures to increase value and efficiency, they are particularly focused on high value innovations – technologies which, if projected benefits and risks are demonstrated, have the potential to significantly improve health outcomes at the same or lower aggregate costs to the health system.

In this context, it becomes clear why the PCAST recommendations for improving drug evaluations could magnify the gap between the evidence that is acceptable for regulatory approval, and the type of evidence that payers and health systems require to assess the effectiveness and value of new drugs. To state it as simply as possible, from a payer perspective it is not particularly reassuring to consider the prospect of increasing numbers of new drugs being approved more rapidly by the FDA with less extensive data on safety and efficacy, as these decision makers come under increasing pressure to provide care that is higher quality, safer and less expensive.

Recommendations

There are a number of strategies that can be explored to minimize the potential headwind to innovation generated by quality/cost/efficiency pressures that characterize the post-regulatory environment. The recommendations below were adapted from a white paper developed in the context of a national gathering of industry and academic leaders hosted by Stanford's Clinical Excellence Research Center to identify private and public policy changes most likely to encourage healthcare innovations that would both improve health and lower US health care spending. A copy of the complete white paper is attached to this testimony.

Consistent and explicit standards of evidence for effectiveness and value

For many years, regulators put sustained effort into defining requirements for safety and efficacy, generally and for specific therapeutic domains and classes of technologies. Payers looking for evidence of effectiveness and value have done relatively little to define the evidentiary requirements, making it difficult for innovators to clearly understand what studies would be adequate to demonstrate effectiveness and value.

There is a need for greater transparency, predictability and consistency in how effectiveness and value of new biomedical technologies is evaluated and paid for by public and private sector payers. Increased transparency and consistency in the evidence requirements for payment across a wide range of public and private payers would significantly reduce payment uncertainty for investors and innovators, decreasing the risk, cost and duration of clinical development programs. Perceived risk within the investment community today is very high, causing a shift of venture funding out of health care. A predictable path to payment could substantially expand the willingness to invest, thereby increasing the development of cost-saving technologies. Simultaneously, clear evidence requirements would strengthen the data available for payers to make payment decisions and provide clearer information to patients and clinicians to make clinical decisions. In addition, the use of standards for inclusion of diverse and/or vulnerable populations in clinical studies would increase knowledge about possible benefits and harms of treatments in these subgroups and subpopulations.

Relevant DHHS agencies should actively seek out and participate in public-private sector initiatives to standardize the evidentiary requirements for demonstrating the effectiveness and value of new biomedical technologies. While general standards are helpful, product developers, investors, and decision makers would benefit most from standards that are developed for major categories of technologies and clinical conditions. The Secretary's Advisory Committee on Genetics, Health and Society had recommended the creation of such a public-private process to develop evidentiary standards for the clinical utility of genetic testing. The logic provided for this recommendation applies equally to other domains of biomedical technology. These standards could be developed by a national and voluntary private sector standard setting body, similar to the Institute of Medicine or the National Quality Forum for example, which serves as a standard-setting body for health care quality measures.

An example of such an activity, in relatively early stages, is the Green Park Collaborative – USA, managed by the Center for Medical Technology Policy. A more detailed overview is attached to this testimony.

Payers can provide coverage contingent on collection of additional data

To generate additional data on longer term clinical outcomes as well as costs and value, public and private payers could expand use of conditional payment mechanisms that link reimbursement to the collection of additional data. With the increased use of accelerated regulatory approval, there will be increasing need for payers to provide coverage while the remaining questions about clinical benefit, safety and target population are addressed. This approach could be deployed more consistently to enable earlier payment for technologies that have substantial potential for reducing costs and improving outcomes. In some cases, late phase and post-approval studies conducted to meet regulatory requirements may also be more efficiently conducted through this approach. A recent White House report on the National Bioeconomy Blueprint recommended increased use of this mechanism to promote the early adoption of potentially high value technologies, and similar recommendations have been advanced by other advisory groups and committees. In May 2012 Medicare held a public advisory committee to explore this approach, and issued updated draft guidance on such an approach - Coverage with Evidence Development (CED) - several months later.

A number of elements are critical to the success of conditional payment programs, most importantly the application of clear criteria for selection of eligible technologies that aim to improve outcomes and lower costs. It is also important to develop a streamlined process to approve study protocols, identify funding sources for research costs, and establish well-defined and reasonable study timelines. Furthermore, there are serious political challenges of withdrawing coverage once it has been provided, though the likelihood of this outcome might be moderated by having clearly defined agreements up front and clear pre-defined outcome and cost targets for retaining coverage. For this reason, it would be particularly important to establish clear benchmarks for outcomes and costs at a defined time period following approval, with a decision made at that point about approving unconditional coverage, retaining the conditional policy, or terminating coverage.

Some work has been done exploring how coverage linked to data collection could be deployed more broadly among private payers. Interest in this approach among private payers would increase if it was clearly designed to promote cost-reducing innovations, and as successful use by Medicare increases. It would be valuable to convene further discussions including Medicare, private payers and other key

stakeholders to explore how the confidence of private payers in this approach could be enhanced. To achieve an acceptable level of efficiency and study sample size, these studies and policies would need to be coordinated across multiple private payers. Should more consistent use of this approach be deployed, it would ideally be coordinated with efforts to expand research infrastructure (as discussed in next recommendation) in order to decrease the cost and increase the efficiency of the studies.

Improve Clinical Research Infrastructure within the Delivery System

A more detailed version of this recommendation is well developed in the PCAST report, though that discussion is targeted to expanding the type of research capacity that is capable of supporting regulatory-quality studies. In order to generate the type of evidence that will inform decisions by payers, health systems, patients and clinicians, it will become increasingly essential to leverage the delivery system itself as a platform for research and other forms of learning. Continued investments in improving research infrastructure, with greater opportunity for life sciences companies to contribute to this development and use this infrastructure to improve the efficiency of conducting clinical studies during the late phases of product development.

While improvements in clinical research infrastructure may require incremental resources, the emphasis of this recommendation is to allow for greater allocation of private sector funds to improve publicly funded research infrastructure. The incentive for such investment would be an understanding that this infrastructure would be made available for private sector funding, subject to well-defined criteria for public health and scientific importance. Several public sector initiatives to expand research infrastructure are already underway, and there should be greater attention leveraging these federal investments with supplemental funding from the life sciences industry. The National Institutes of Health, for example, funded a Health Care System Collaboratory that is supporting partnerships with integrated delivery systems "...to strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners". While the seven initial Collaboratory demonstration projects are federally funded and do not involve partnerships with product developers, the model could readily be expanded to support private sector clinical studies. Similarly, the Patient-Centered Outcomes Research Institute has recently launched a national patient-centered clinical research network call PCORnet, which is being formed out of what are currently 29 separate research networks. This initiative has great potential to provide the sort of practice-based research infrastructure to support the efficient generation of evidence of effectiveness and value for both

An important benefit of expanding the capacity to conduct clinical research within the health care delivery system is the ability to increase the representation of diverse populations in clinical trials (age, racial, ethnic, socioeconomic, genetic, etc.), in part to have better evidence about effectiveness of treatments in various subpopulations.

Conclusion

The PCAST report on Innovation in Drug Development contains a number of thoughtful, well-crafted and potentially impactful recommendations for translating several decades of basic science discoveries into new therapies for high priority health needs. Several of the key recommendations in the PCAST report (recs 3,4,5) focus on policy mechanism to speed up the evaluation of new drugs. These recommendations have the potential to considerably reduce the time and cost required to complete trials and obtain regulatory approval for pharmaceutical and biotech products targeted to important unmet health needs. They also create a new challenge from the perspective of post-regulatory decision makers: payers, health systems, clinicians, patients and others. It is unclear at this point, and was not discussed in detail by PCAST, how the payers, health systems and other post-regulatory decision makers might react to the proposed mechanisms for more rapid regulatory approval. From a payer perspective it is not particularly reassuring to consider the prospect of increasing numbers of new drugs being approved more rapidly by the FDA with less extensive data on safety and efficacy, as they come under increasing pressure to provide care that is higher quality, safer and less expensive. There are a number of approaches that can be taken to minimize the potential headwind to innovation generated by the post-regulatory environment:

- Consistent and explicit standards of evidence for effectiveness and value
- Payers can provide coverage contingent on collection of additional data
- Improve Clinical Research Infrastructure within the Delivery System

It would be useful to bring together the PCAST members and external experts that helped to develop this innovation report with a broader range of experts and stakeholders, particularly drawing from the universe of post-regulatory decision makers, to discuss the pros and cons of these and other strategies to ensure that the dynamics of biomedical innovation and health systems reformed are aligned to the greatest extent possible.

Thank you again for the opportunity to testify today. I would like to submit for the record the white paper on biomedical innovation and information on the Green Park Collaborative mentioned above.

Report to the White House Office of Science and Technology Policy

Biomedical Innovations: *What modifications in public and/or private policies affecting research on biomedical innovations would most rapidly lower US health care spending growth without adversely affecting health ?*

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BACKGROUND

Biomedical technology is both a positive contributor to the US economy and a driver of higher rates of health care spending growth. While historical experience supports the view that the net effect of new technology is to increase health care spending over time, certain new technologies offer the potential for improvements in clinical outcomes *and* lower aggregate health care spending. To retain the economic and health benefits of biomedical innovations while reducing health spending, biomedical research policies that favor both objectives must be more highly prioritized.

Framework for Recommendations

Our panel on biomedical innovation analyzed possible options within the context of three broader policy considerations:

Payment reform to reward value of care is essential: Any policy intended to promote biomedical innovation will only result in significant reductions in costs and better outcomes in the context of successful payment and delivery system reforms. Constructive reforms will almost certainly need to include payment policies that are linked to improving the value of health care, rather than volume of care. Within the current system, biomedical innovations that improve quality and save costs, such as some minimally invasive surgical techniques or targeted therapeutics, will often have the net effect of increasing spending because of pervasive financial incentives to provide more services, and the rarity of incentives for coordination of care delivery and other proven methods of improving value. Biomedical innovation alone cannot improve outcomes and reduce costs unless forms of payment that reward value become dominant within both publicly and privately funded health care.

Useful prior recommendations to improve value have been offered but not implemented: Mindful that many groups have wrestled with the general question of how to improve quality while reducing costs of care, in some cases with specific attention to biomedical innovation, we looked to highlight and build upon existing reports and recommendations. Each of the selected recommendations is presented here because it has not yet been implemented, but we consider each to be high priority. In selecting recommendations that have been more fully developed elsewhere, we are able to refer to reports in which the issues and the steps necessary to implement those recommendations have already been considered in substantial detail.

Solutions must be cost-neutral to public sector: We focus on research policy recommendations that would require little or no incremental public sector spending beyond resources already committed. Our rationale is that the public will not likely provide substantial new research resources and that reprogramming research dollars away from existing programs is politically difficult and probably unwise. In addition, it is uncertain which current uses of public funds for research are less important than what is suggested here. Furthermore, we believe it is feasible to produce better clinical results at current levels of health spending or the same results with less spending. In that spirit, we avoided recommendations that promoted near term increases in spending on research with a promise of long term reduction in health care costs.

RECOMMENDATIONS

Recommendation 1: Develop and apply consistent evidence standards for payment across payers. There is a need for greater transparency, predictability and consistency in how effectiveness and value of new biomedical technologies is evaluated and paid for by public and private sector payers. Increased transparency and consistency in the evidence requirements for payment across a wide range of public and private payers would significantly reduce payment uncertainty for investors and innovators, decreasing the risk, cost and duration of clinical development programs. Perceived risk within the investment community today is very high, causing a shift of venture funding out of health care. A predictable path to payment could substantially expand the willingness to invest, thereby increasing the development of cost-saving technologies. Simultaneously, clear evidence requirements would strengthen the data available for payers to make payment decisions and provide clearer information to patients and clinicians to make clinical decisions. In addition, the use of standards for inclusion of diverse and/or vulnerable populations in clinical studies would increase knowledge about possible benefits and harms of treatments in these subgroups and subpopulations.

Relevant DHHS agencies should actively seek out and participate in public-private sector initiatives to standardize the evidentiary requirements for demonstrating the effectiveness and value of new biomedical technologies. While general standards are helpful, product developers, investors, and decision makers would benefit most from standards that are developed for major categories of technologies and clinical conditions. The Secretary's Advisory Committee on Genetics, Health and Society had recommended the creation of such a public-private process to develop evidentiary standards for the clinical utility of genetic testing.[1] The logic provided for this recommendation applies equally to other domains of biomedical technology. These standards could be developed by a national and voluntary private sector standard setting body, similar to the Institute of Medicine or the National Quality Forum for example, which serves as a standard-setting body for health care quality measures.

Once these standards are developed, all publicly funded health care programs (Medicare, Veterans Administration, Medicaid, etc.) should be required to apply these evidentiary standards for payment decision making. Policy mechanisms should also be explored by which private payers could be very strongly encouraged or even required to apply these standards, such as through rules adopted by state-based Health Insurance Exchanges or ERISA-qualified health plans.

A salient example of a toolkit of measurement instruments designed for studies of neurological and behavioral health is the NIH Toolkit for Assessment of Neurological and Behavioral Function.[2] This resource was developed with to improve cross-study comparisons and provide standards for large longitudinal studies. Administration of all of the measurement instruments in this toolkit requires nearly two hours, suggesting that a process using a more limited core set of measures might be useful to assess biomedical technologies in the context of payment decision making. One example of this type of core set of recommended outcome measures was recently reported in the Journal of Clinical Oncology.[3]

The high level of support for the MolDx program[4] for payment of molecular diagnostics, developed by Palmetto GBA to support their clinical policy decisions for Medicare, underscores the popularity of efforts by payers to apply well-defined standards for coverage and payment decisions.

In addition to standards for evaluating effectiveness, there is also a need to develop standards for measuring value (health outcomes achieved per dollar spent). A considerable amount of work on measuring value has been done in support of the movement in the UK toward value-based pricing. [5] Further methodological research into robust approaches to determine incremental value, and processes to secure broad stakeholder consensus around those methods, would be important to making fair and transparent pricing decisions.

Recommendation 2: Expand Use of Coverage with Evidence Development. Expand use of conditional payment mechanisms, such as Coverage with Evidence Development (CED), by Medicare and other publicly funded health insurance programs, tied to the conduct of research that would confirm the impact of promising biomedical innovations on health outcomes and costs. This approach could be deployed more consistently to enable earlier payment for technologies that have substantial potential for reducing costs and improving outcomes. In some cases, late phase and post-approval studies conducted to meet regulatory requirements may also be more efficiently conducted through CED. A recent White House report on the National Bioeconomy Blueprint[6] recommended increased use of this mechanism to promote the early adoption of potentially high value technologies, and similar recommendations have been advanced by other advisory groups and committees. In May 2012 Medicare held a public advisory committee to explore this approach, and issued updated draft guidance on Coverage with Evidence Development (CED) several months later[7].

A number of elements are critical to the success of conditional payment programs, most importantly the application of clear criteria for selection of eligible technologies that aim to improve outcomes and lower costs. It is also important to develop a streamlined process to approve CED study protocols, identify funding sources for research costs, and establish well-defined and reasonable study timelines. Furthermore, there are serious political challenges of withdrawing coverage once it has been provided, though the likelihood of this outcome might be moderated by having clearly defined agreements up front and clear pre-defined outcome and cost targets for retaining coverage. For this reason, it would be particularly important to establish clear benchmarks for outcomes and costs at a defined time period following approval of CED, with a decision made at that point about approving unconditional coverage, retaining the CED policy, or terminating coverage. Value-based pricing of technologies and services could inform the initial prices paid for technologies when introduced under CED, and results of the completed studies would inform future adjusted pricing.

Some work has been done exploring how CED could be deployed more broadly among private payers[8]. Interest in this approach among private payers would increase if it was clearly designed to promote cost-reducing innovations, and as successful use by Medicare increases. It would be valuable to convene further discussions including Medicare, private payers and other key stakeholders to explore how the confidence of private payers in this approach could be enhanced. To achieve an acceptable level of efficiency and study sample size, CED studies and policies would need to be coordinated across multiple private payers. Should more consistent use of CED be deployed, it would ideally be coordinated with efforts to expand research infrastructure (as discussed in recommendation 3) in order to decrease the cost and increase the efficiency of CED studies.

Recommendation 3: Improve Clinical Research Infrastructure. Continue investments in improving research infrastructure, with greater opportunity for life sciences companies to contribute to this development and use this infrastructure to improve the efficiency of conducting clinical studies during product development. The President's Council of Advisors on Science and Technology 2012 report on Innovation in Drug Development identified inefficiency in clinical trials as a major barrier to efficient innovation, and recommended the establishment of a broad based public-private partnership that would improve clinical trials capabilities.[9] The IOM Roundtable on Drug Discovery focused extensively on the need for improvements in the clinical research infrastructure, and has produced a number of reports that clearly describe limitations of the current system, as well as steps necessary for improvement.[10]

While improvements in clinical research infrastructure may require incremental resources, the emphasis of this recommendation is to allow for greater allocation of private sector funds to improve publicly funded research infrastructure. The incentive for such investment would be an understanding that this infrastructure would be made available for private sector funding, subject to well-defined criteria for public health and scientific importance. Several public sector initiatives to expand research infrastructure are already underway, and there should be greater attention leveraging these federal investments with supplemental funding from the life sciences industry. The National Institutes of Health, for example, recently funded a Health Care System Collaboratory that is supporting partnerships with integrated delivery systems "...to strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners".[11] While the seven initial Collaboratory demonstration projects are federally funded and do not involve partnerships with product developers, the model could readily be expanded to support private sector clinical studies. Similarly, the Clinical and Translational Science Award program of the NIH could be expanded to enable private sector clinical development activities; supplemental private sector funds could support expansion of the clinical research infrastructure for both publicly and privately funded studies.

Useful insights into effort to expand clinical research infrastructure within the health care delivery system are also available in a 2011 report that describes a pathway for more efficiently conducting clinical research with the British National Health Service.[12] Rapid developments in improving the quality and availability of data routinely generated through the delivery of clinical care also offers important opportunities to efficiently learn about the benefits, harms and costs of new technologies as they are adopted in clinical use. An important benefit of expanding the capacity to conduct clinical research within the health care delivery system is the ability to increase the representation of diverse populations in clinical trials (age, racial, ethnic, socioeconomic, genetic, etc.), in part to have better evidence about effectiveness of treatments in various subpopulations.

A more radical proposal would be a call for increased private sector investment in both clinical and basic research infrastructure. This notion recognizes the private sector's economically-driven pullback from in-house discovery research and its increased dependence on robust public support of basic research. While the ROI for improved cost-effectiveness of health care is on a long timeframe here, it is nevertheless direct as documented in the 2011 NRC report "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease", and policies should reflect this critical linkage.

Recommendation 4: Use current evidence and analyses to test an initial approach to promoting diagnostics in personalized medicine likely to safely lower annual health spending growth. There may be substantial potential for improving health outcomes and reducing costs through molecular diagnostics to identify subsets of patients who will have large benefits or significant risks from specific treatments. Results from diagnostic tests drive a large fraction of treatment decisions but the tests account for a small fraction of total health care spending, and there is great potential leverage in using new diagnostics to better guide treatment decisions. While there is limited evidence that the adoption of these diagnostics in clinical care lead to reduced spending,[13] it is clear that the ability to identify more accurately those patients who will benefit most from a particular treatment offers the potential to avoid costly treatments in those who will not benefit, or who may be harmed. The realization of these health improvements and cost savings will hinge on the payment levels of the tests and treatments, as well as the actual outcomes of the decisions made by patients and clinicians when provided with the test results. However, robust adoption of payment reforms and pricing methods that reward value rather than volume, as discussed above, can assure realization of cost savings.

A fundamental challenge to the evidence-based adoption of new molecular diagnostics is the difficulty, cost and uncertainty associated with generating persuasive evidence of clinical validity and clinical utility. Regulators and payers have not yet provided a clear and consistent evidence-based framework for oversight of molecular and genetic diagnostics, leading to considerable uncertainty among diagnostics companies and their investors regarding the expected cost and duration of product development. Concerns have also been raised about the cost and time required to generate evidence of clinical validity and utility with the level of certainty expected by some payers and guideline developers.

Each of the three research policy recommendations described above may be helpful in promoting the efficient generation of evidence on the clinical validity, utility and value of molecular diagnostics. Some of the programs conducted under the Foundation for the National Institutes of Health, such as the I-SPY[14] and I-SPY 2 trials[15] may be important models to replicate beyond breast cancer. These programs involve pre-competitive collaboration across multiple life sciences companies, as well as adaptive trials design methods, to support the rapid development of biomarker guided therapy. Additional efforts in this direction would be valuable.

A series of reports issued by the Roundtable on Translating Genomic-based Research for Health[16-18] over the past five years describe the range of barriers to the development and use of molecular diagnostics in health care as well as promising approaches to overcome these barriers. Numerous other reports have addressed the evidentiary, regulatory and payment issues associated with this class of technologies. Given the rapid scientific development in this field, the accelerated rate of commercial development, and the unique potential for these diagnostics to improve health while reduce spending, a careful review of this body of work for actionable research policy recommendations would be worthwhile.

Creation of a knowledge network that merges, and permits interrogation and analysis of molecular data with social and behavioral data (including EMR) should facilitate discoveries. Other important research policy strategies include interoperability standards for biomedical research databases, natural language processing and machine learning protocols to integrate existing databases, simple but secure blanket

consenting for all patients to provide their personal health data for research, certification of digital health devices and applications (increasingly, the "molecular diagnostics" referred to in the present recommendation) for sensing and reporting physiologic and molecular data in the course of normal life, establishment of molecular data collection and analysis facilities in CLIA environments.

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Green Park Collaborative | USA

A collaborative for innovation and effectiveness

Green Park Collaborative – USA
A New Partnership to Guide Health Care Innovation

Winter 2014

The Center for Medical Technology Policy launched the Green Park Collaborative – USA (GPC-USA), a multi-stakeholder forum that develops condition and technology-specific study design recommendations, to guide the generation of evidence needed to inform both clinical and coverage and payment decisions in the United States. Launched in May 2013, GPC-USA is led by CMTP Senior Program Director Elisabeth Houtsmuller, PhD. CMTP Founder and CEO Sean Tunis, MD, MSc, chairs its Advisory Committee (see page 3).

GPC-USA includes a diverse mix of payers, life sciences companies, patients, clinicians, researchers, regulators and other stakeholders. Currently, this group focuses on methodological standards in oncology and endocrine and metabolic diseases.

The Challenge: Generating Clinical Evidence that Matters

During the past decade, there has been increasing emphasis on generating evidence of effectiveness and value that payers need to make decisions, while also providing useful information for patients, consumers, clinicians, and other health care decision makers. Intensifying cost pressures and new models of shared risk (such as accountable care organizations) are driving all of these stakeholders to pay increasing attention to comparative effectiveness and value when making choices between existing health interventions and newer alternatives.

While aware of these trends, life sciences companies and other clinical researchers have limited information about what specific additional evidence payers and other decision makers need. Product developers also worry that generating this additional evidence may significantly increase the cost and duration of clinical development and impede the pace of health care innovation. The result: broad uncertainty about how best to develop and test new interventions.

In order to generate better evidence of real world benefits and harms while sustaining innovation, it is critical to reduce this ambiguity. Where possible, the evidence requirements for reimbursement and clinical benefit should be clearly and consistently defined for specific conditions and classes of technologies.

Regulatory bodies, like the FDA, typically provide this kind of guidance on study design to life sciences companies — focused on the requirements for regulatory approval. However, there is no analogous organization that can provide clear guidance to researchers and life sciences companies reflecting reimbursement requirements. Health plans have limited technical capacity and resources to devote to this work. And while the Patient-Centered Outcomes Research Institute (PCORI) is developing general methods standards for Comparative Effectiveness Research (CER), it does not intend to develop standards for specific clinical conditions or categories of technology.

Intensifying cost pressures and new models of shared risk are primary drivers making payers, clinicians and patients increasingly attentive to comparative effectiveness and value when making choices between existing health interventions and newer alternatives

Towards a Solution: The Green Park Collaborative - USA (GPC-USA)

The GPC-USA provides a neutral forum where experts, stakeholders and decision makers can discuss and develop condition-specific methodological standards for clinical research that evaluate real world effectiveness and value. Much of the work of this Collaborative takes place in face-to-face workshops structured to support the sustained and informed discussion necessary to achieve deep and shared understanding of these complex issues.

Much of the work of this Collaborative takes place in face-to-face workshops structured to support the sustained and informed discussion necessary to achieve deep and shared understanding of these complex issues.

The main products of the GPC-USA are ***Effectiveness Guidance Documents (EGDs)***, which provide specific recommendations for the design of prospective clinical studies. These reflect the evidence expectations of payers, informed by the perspectives of patients, clinicians and other decision-makers. EGD recommendations address critical domains of study design including:

- Patient inclusion/exclusion criteria,
- Important subpopulations,
- Choice of comparators,
- Primary and secondary outcomes,
- Duration of follow-up,
- The magnitude of clinically meaningful differences, and
- Other study design elements of significance to specific conditions and/or technologies.

For example, a 2013 EGD described a core set of 14 patient-reported symptoms that should be included in all trials of adult oncology drugs, as well as the data collection schedule and process. A second EGD focused on the clinical utility of molecular diagnostics in oncology that established study design recommendations for these advanced diagnostics. Currently, GPC-USA is developing EGDs around Patient-Centered Outcomes in Diabetes, Place in Therapy in Cancer Treatment, and Next Generation Sequencing in Oncology.

The recommended standards developed through an EGD's multi-stakeholder collaborative process provide a range of decision makers with well-defined study design "benchmarks" that they can use when assessing the quality and relevance of clinical studies including:

- Payers making coverage and pricing decisions;
- Medical professional societies developing clinical guidelines;
- Research funding agencies evaluating grant proposals; and
- Organizations producing educational material for patients and consumers.

Condition-Specific Consortia

In its first year, the GPC-USA has established two Consortia in the following priority areas:

- Endocrine and Metabolic Diseases, led by C. Daniel Mullins, PhD, at the University of Maryland School of Pharmacy
- Oncology, led by Donna Messner, PhD, Research Director at CMTP

Consortia conduct their work through in-person, multi-stakeholder workshops, video/web supported conference calls, and electronic communication. Each Consortium will complete its EGDs in approximately 12 months, and all final guidance documents will be made publicly available. Potential conditions for future Consortia include mental health disorders, spine pain and injury, cardiovascular disease, pulmonary disease, infectious disease (hepatitis C, antibiotics, etc.) and others to be selected based on input from GPC-USA members.

Participants in GPC-USA Consortia activities include invited patients, consumers, caregivers, practicing clinicians, payers and health technology assessment groups, researchers, methodologists, life sciences companies, professional society representatives and other key experts and stakeholders. In addition, appropriate experts from the FDA, National Institutes of Health (NIH), Centers for Medicare and Medicaid Services (CMS), and the Veterans Administration also participate. A core premise behind the GPC methods standards development process is that the participation of a broad range of stakeholders

improves the likelihood of achieving a reasonable balance of validity, relevance, feasibility, and timeliness in the design of clinical studies. To make this possible, Consortia work deliberately to create trusting, collaborative, and transparent environments, where these candid and difficult conversations can occur.

GPC-USA guidance documents are also informed by, and aligned with, existing methodological standards and guidance, including those produced by the FDA, PCORI, the Agency for Healthcare Research and Quality (AHRQ), and others. Over time, guidance documents will be updated to reflect advances in knowledge about the clinical condition, improvements in health technologies and refinements in research methods.

Some other examples of completed Effectiveness Guidance Documents are posted on CMTP's web site.

Advisory Committee

The work of the GPC-USA is guided by an Advisory Committee representing payers, purchasers, patients, consumers, clinicians, researchers, regulators and policy makers. This group provides general oversight of the technical work of the GPC-USA, including modifications to the process for developing methodological standards, as well as refinements to the structure and governance of the enterprise. The GPC Advisory Committee also helps to prioritize and select topics for EGD development, develop dissemination strategies, and advise on mechanisms to promote adherence to final recommended standards.

Joining Us

Participation in the GPC-USA is by invitation only and allows your organization to be an active participant in defining methodological standards for clinical research, CER and PCOR in clinical domains of high unmet health needs. Through a multi-stakeholder dialogue, you can help to develop and contribute to a deep understanding of how best to generate or use relevant, credible evidence for these important clinical conditions. You and other GPC-USA participants have a voice at the table as these critical issues are discussed and debated, and you gain deep insights into the perspectives of other stakeholders through the in-person working meetings, calls and electronic communication.

GPC USA Advisory Committee

SEAN TUNIS, MD, MSc (Chair)
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ROBERT TEMPLE, MD
Food and Drug Administration

If you are a payer, clearly defined evidentiary standards improve the quality and relevance of studies available for coverage, coding, and payment decisions. In addition, basing such decisions on standards that were defined in advance through a transparent, multi-stakeholder process provides a stronger foundation to defend these decisions.

Patients and clinicians also benefit from improvements in the quality, relevance, and consistency of health research resulting in better evidence of effectiveness, safety, and value. Our belief is that more relevant and applicable evidence will improve the decision-making processes in our healthcare system and also lead to better health outcomes.

If you are a life sciences company, you benefit from greater certainty about the evidence needed to demonstrate the value of new health care innovations. Life sciences companies also benefit by having greater clarity and predictability regarding the evidence expectations and preferences of patients, clinicians, payers and other decision makers. This should support greater confidence at all phases of the clinical development process, including very early resource decisions about whether to pursue further clinical development.

Key benefits

- Participation in a solicitation of potential clinical topics for EGD development
- Participation in meetings of one or more disease-specific Consortia
- Eligibility to provide technical experts to serve on EGD methods standards technical working groups
- Preview of clinical topics and draft guidance documents prior to public distribution
- Participation in comment periods for EGDs
- Attendance at an annual GPC-USA membership meeting, in the Fall of 2014, that will be focused on CER generally, with Consortia-specific sessions, including progress reports and 2015 priority setting
- Eligibility to serve on the GPC-Advisory Committee
- Recognition as a participant in the development of EGDs in all publicly released communications (subject to approval).

For more information about GPC membership, contact Corinne Warren at CMTP.

CMTP

Center for Medical Technology Policy (CMTP)

The Center for Medical Technology Policy (CMTP) is an independent, non-profit 501(c)(3) organization that aims to make health care more effective and affordable by improving the quality, relevance, and efficiency of health care research. We focus on the design and implementation of comparative effectiveness research to produce information that helps patients, clinicians, and payers make informed treatment and policy decisions. CMTP provides a trusted forum in which a broad range of stakeholders can collaborate to identify important research questions, design appropriate studies, and develop innovative partnerships to implement these studies.

GPC-USA and Green Park Collaborative International (GPC-I)

The work of the GPC-USA is informed by CMTP's experience managing GPC-International, a partnership between Health Technology Assessment International (HTAi) and CMTP. A GPC-I pilot project on Alzheimer's Disease assessed the feasibility of developing global guidance for the life sciences industry on the design of clinical studies to meet the needs of Health Technology Assessment (HTA) and coverage bodies. This project was completed in the Spring of 2013. Those wishing to learn more about GPC-I should contact Corinne Warren at CMTP: corinne.warren@cmtpnet.org.

Mr. PITTS. The Chair thanks the gentleman. Thanks all the witnesses for their prepared testimony. We will now begin questions and answers. I will begin the questioning and recognize myself 5 minutes for that purpose.

Dr. Neil, the PCAST report notes that the pharmaceutical industry is facing the largest patent cliff in its history. As a result, many companies are adopting more conservative approaches to research and development, particularly in areas with growing healthcare and economic burden, such as neurodegenerative diseases such as Alzheimer's and psychiatric diseases. What role could additional economic incentives play in driving R&D into these areas where there is a critical public health need, Dr. Neil?

Mr. NEIL. I think they could be extremely valuable in helping to offset some of the cost associated with the risk, and the length of time these programs require. I do think though that it may be as productive or more productive to invest additional resources in things like endpoints, intermediate clinical endpoints, clinical endpoints. Often, we have found that as we try to study some of these neurodegenerative diseases, they—it is a very long time between onset and ultimate disability, and if that is what needs to be used as an endpoint, it makes the feasibility of these trials much lower. So we haven't done enough to really invest, I think, in creating such endpoints, and I am thinking about Alzheimer's Disease, I am thinking about stroke as a couple of those, but there are many others, and some of the rarer neurodegenerative diseases have been inadequately studied with respect to their natural history as well. So I think some targeted efforts there would also be very helpful, as well as accelerating the pace of discovery work where diseases like schizophrenia, we have been out of really promising targets for some time.

Mr. PITTS. OK. Ms. Radcliffe, what challenges do drug sponsors and the FDA face today in the use of surrogate endpoints and biomarkers, and what are the current barriers to their more widespread adoption and use? And maybe you want to, just for the general public, tell us what biomarkers, endpoints, define them for us too briefly.

Ms. RADCLIFFE. Sure. Absolutely. So biomarkers, and the terms biomarkers and endpoints are used in various different ways in the scientific community, so I am going to tell you the way in which I urge that we understand those terms. A biomarker is really a signal of—it is a biological signal of another biological process. It is really that simple. A biomarker can be used in many different ways in research and development. For it to be used in the regulatory context, all parties have to have a great confidence in the relationship between the biological signal and the biological process that it is signaling. An endpoint in regulatory terms, a clinical endpoint, is something that affects how a patient feels, functions or survives. So in relatively simple terms, it is something that the patient will actually recognize. A surrogate endpoint is a marker that can point toward the ultimate clinical benefit for a patient. So an example of that would be viral load is a surrogate endpoint for a treatment effect for HIV and AIDS drugs. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier on in the disease process. And so an example of an intermediate clinical endpoint

would be something that is called forced vital capacity, that is the ability for a patient to expel a large amount of air, and it can be a good marker of progression and possibly treatment effect in neurodegenerative disorders. And so the use of intermediate clinical endpoints can expedite drug development because you are now working toward treatment of an endpoint that you are seeing earlier on in the disease process, and that may enable you to ward off further—effects further down the line in the disease process. So why is it important for our companies? The use of surrogate endpoints and intermediate clinical endpoints can expedite drug development, and enable us to get a product to patients earlier with smaller and shorter clinical trials. In terms of the obstacles that we face, as I said, there is not the kind of clarity that we would like around what FDA will accept as a surrogate endpoint, and what FDA will accept as an intermediate clinical endpoint. The evidentiary standards that FDA is likely to require at this time really require a lot more discussion with the Agency, and also just in terms of process, as I said in my testimony, there isn't at this time a good practice of companies and sponsors talking about intermediate clinical endpoints earlier on in the drug development process, so that you can really work toward the use of those endpoints as you develop your submission to the FDA.

Mr. PITTS. The Chair thanks the gentlelady.

My time has expired. Recognize the ranking member 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to explore in some detail one of the recommendations from the PCAST report, specifically, recommendation number three, which states that FDA should expand the use of its existing authorities for accelerated approval, and for confirmatory evidence. And as I understand it, there are already a few pathways in the current law and regulations for the expedited review of drugs, including fast track, breakthrough therapy, accelerated approval and priority review, and the goal of all these pathways is to speed the development and availability of new treatments to patients at the earliest possible time. Just a couple of years ago in the 2012 FDA Safety Innovation Act, we updated the fast track approval mechanism and established the breakthrough therapy path. And then, of course, the 21st Century Cures Initiative seems to have been promoted at least in part by what has been described as a regulatory system that is a relic of the past, but this is confusing to me because we just finished updating the system, and providing FDA with new tools. So I also didn't hear anyone at this—the first roundtable with the 21st Century Cures Initiative who would describe FDA's drug regulatory program as somehow out-of-date.

So I would like to hear more from our experts here today on how effectively FDA has been using these current authorities, and where there might be room for improvement.

First, let me ask Dr. Allen. Your testimony describes FDA's use of the breakthrough therapy pathway, which sounds like it has been a real success. Can you say a little more about that, and describe how FDA has used any of the other expedited review authorities with respect to cancer drugs, and have you identified any problems or issues in its application of these authorities?

Mr. ALLEN. Sure. Well, I again want to thank the committee for their leadership in creating such a designation.

The tools that FDA currently has, based on the 2012 law and others, have been widely used in cancer. I think well over a third of all anticancer drugs have utilized the accelerated approval process, for example. So it certainly is valuable. The purpose of the breakthrough therapy designation was to, as you say, Mr. Pallone, too, advance and give the flexibility for FDA to respond to the current state of science, because what we are seeing in oncology and many other genetically driven diseases is the ability to target different genetic alterations, and stop the progression of the disease. And this calls for a different way of doing business, and we believe that is what the FDA is doing, and they have robustly implemented the new breakthrough therapies provision and are excising it regularly.

I think it is worth noting the resource intensity of this program. It certainly is serving its purpose of getting the most promising therapies to patients, but the resources required to do so are not insignificant, and I know there is a hearing elsewhere today considering the funding for FDA, and I would encourage them to do what they can to support that.

I think the historic basis of speaking to those regulations is because there were laws in 1960 that established the safety and efficacy standard, and those are extremely important that we continue to optimize regulation and drug development within those important standards.

Mr. PALLONE. All right, thanks.

Mr. Sasinowski, your testimony also describes the ways in which FDA has used these authorities over the years, and it sounds like you would also say that FDA uses them frequently and prudently. Is that correct?

Mr. SASINOWSKI. Mr. Pallone, prudently but not frequently. The analysis that my colleague, Alex Verone, and I did, we looked at all of the FDA accelerated approvals for therapies other than cancer, and Mr. Allen is right, it is often used in cancer. I was at FDA during the AIDS crisis, and so I was part of the group that helped create Subpart H, which was very useful for stemming the AIDS crisis. So accelerated approval has been used, but you will notice in our PCAST report that you cite, Mr. Pallone, that 87—we say in the PCAST report 87 percent of all the accelerated approvals have been for cancer and for AIDS. And so what Mr. Verone and I did is we looked at every accelerated approval from the mid-'80s through June 2013. We found only 19 drugs that had been approved, not for cancer, not for AIDS, under accelerated approval. We found that the FDA did use accelerated approval appropriately in those 19 cases, but it was only 19 cases, Mr. Pallone, and that is why I think PCAST said we should use it more. I think that is why this committee and Congress said in FDASIA, FDA, use it more. That is why there are 2 women who I was surprised to see here, who are in this room, who have between the 2 of them, 3 boys with DMD; Christine McSherry and Jane McNeary, and I know that they represent, as a member of NORD, they represent the kind of Americans who are suffering and who are looking for FDA

to use accelerated approval more often for conditions that are not AIDS, not cancer.

So I think appropriately they used it, and that is why I suggest this chart, because I have been to thousands of FDA meetings since I left the FDA, with sponsors seldom does the word Subpart H, accelerated approval or fast track ever get mentioned. People are not focused on it, that is why I urge you to consider exhorting the FDA through some simple mechanisms like a chart, like at every advisory committee when the chair of an advisory committee turns to the FDA and says, "What are we supposed to do with this date? We know what the Congress' standard was in 1962: two adequate and well-controlled studies. This is a rare disease. Something like Duchenne Muscular Dystrophy. We don't have two adequate and well-controlled studies, so what are we supposed to do?"

Well, there is a lot of hemming and hawing, and I think that if we had a chart like this that was proposed, that would summarize in a clear way that there are alternate authorities like the 1997 authority that Congress created, which was the single study with confirmatory evidence, and I have explained that in great detail in my written testimony, that that would be very useful, as well as to remind everybody of accelerated approval.

Mr. Pallone, I was at a hearing just last summer, in August 2013, for a drug for autosomal dominant polycystic kidney disease. My spiritual director had his nephew die of this disease. I know people who have died of this rare disease. It is a terrible disease, and yet not once did anyone ever mention at that hearing the possibility of accelerated approval, even though it is a serious disease, it is for a situation where there are no approved therapies, it is ripe for consideration under accelerated approval, just like PCAST, just like you and FDASIA said FDA should do, and yet it was never considered.

So I am struggling to think of ways, Mr. Pallone and the committee, to try to bring this forward in practical ways, and that is why I come up with something as simple as a chart. It might seem pedantic, it might seem trite, but I think sometimes simple things work. And so I think you are right when my analysis shows that the FDA has used this authority appropriately and prudently, but not frequently. And the other thing that has been completely overlooked is that single study with confirmatory evidence standard, which Congress created in 1997 and FDA seldom used.

Mr. PALLONE. Thank you.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the vice chair of the subcommittee, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. Thank you, Mr. Chairman. And I actually appreciate that last part of your discussion, Mr. Sasinowski. You started at the FDA just a couple of years after I started in private practice, and I can recall back in the '80s being frustrated by the fact that it seemed like there were new therapies that were available in Europe, and it took us forever to get them in this country. Of course, Chairman Waxman, or Ranking Member Waxman, deserves a lot of credit for starting the user fee agreements, which we reauthorized in the last Congress.

Dr. Neil, I wanted to ask you just very quickly if you could—you mentioned that your company was involved in novel ex vivo gene therapies. Could you give us a synopsis or a summary of—without violating, obviously, propriety interests, but can you tell us some of the directions that you are—in which you are working?

Mr. NEIL. Yes. The core of our technology is something called the bio pump. So we remove a small piece of dermis, the layer just below the skin, about half the size of a toothpick, and we transduce that with a viral vector to express a transgene, a protein that a patient with a rare and orphan disease might not express at all, or might express in too low a quantity, and it is causing their disease, and they could benefit from having this restored. And after the transduction, all of the viral antigens are washed away and we reimplant this small piece of tissue back into the patient, so the patient effectively manufactures their own protein that they could not manufacture before, or in a sufficient quantity, and that then addresses, we hope, the disease in question.

And we are aiming this technology at a number of rare and orphan diseases that could benefit.

Mr. BURGESS. And in addition to rare diseases, are there more common diseases that you are also working toward?

Mr. NEIL. Yes, that is very likely, but I think that we shouldn't overlook the fact that very often we can learn so much by studying a rare and orphan disease initially because the population is enriched, we understand the mechanisms much better, and then we can apply the lessons that we have learned to the larger syndromic diseases.

Mr. BURGESS. Since a lot of this panel, or a this hearing today, deals with the regulatory aspects, how is that—how has your experience been then when you take this information back to the FDA for regulatory approval? Do they understand what you are doing, are they able to give you the proper direction about how to structure your studies so that regulatory approval can be achieved?

Mr. NEIL. Yes, our interactions with FDA have been a little bit earlier than approval, because we are just embarking on some of these programs in the clinic, but those interactions have been very positive, and they seem very helpful and very interested in the technology, but we and other companies are now bringing to FDA very novel therapies which incorporate many different elements, such as medical devices, gene therapy, tissue transplant and so on, and I think that, and I directed some of my testimony toward that, the increasing complexity of these types of treatments, something that FDA is going to need to invest in expertise in——

Mr. BURGESS. That is——

Mr. NEIL [continuing]. Culture.

Mr. BURGESS. That is correct. I don't mean to interrupt you because I am going to run out of time, but that is correct, they don't have the——

Mr. NEIL. Right.

Mr. BURGESS [continuing]. Expertise currently. They do have to develop it.

Dr. Tunis, I really appreciated your end of the discussion. You talked about from the payer aspect to the CMS aspect. Certainly we want to avoid the public relations disasters that were of Asten

and Provenge from a year or two ago, and one of my concerns through a lot of the hearings that we have had here is anyone looking at the end use of this, I mean, OK, we have got NIH developing, we have got the FDA which is going to regulate and/or approve, but we also need to involve the payer at some point to let them know what is coming so that they can appropriately adjust. So I do appreciate you bringing that up, and I think oftentimes we overlook that aspect of the regulatory pathway.

Mr. NEIL. Yes, and, you know, I think, just to point out, I think, you know, the payers are often viewed collectively as, you know, not in favor of innovation or somehow resistant to, you know, new technologies, and while, you know, there are certain ways in which that is true, I think it is also true that the health system understands that innovation is potentially a way to get better outcomes at even lost costs, you know. Treating disease is obviously, you know, cheaper than treating a—you know, treating it forever is cheaper than having to continue to treat it in an ongoing way.

So the challenge really is that—and as I said, I do think the payers get left out of these conversations. There were a couple of payers on the PCAST committee, and again, most of the discussion about the—is about regulatory issues, but, you know, a metaphor I use is you don't want to create this superhighway of innovation in the regulatory space, and then have a gravel road, you know——

Mr. BURGESS. Um-hum.

Mr. NEIL [continuing]. In the reimbursement space for those——

Mr. BURGESS. And I have been down that gravel road. You know, when I was in medical school, we learned about the treatment of peptic ulcer disease. It was a surgery, a highly selective vagotomy of removal of part of your body, but I also remember going to a luncheon meeting back in the '70's where Dr. Fordtran from Dallas came down and talked about this new idea he had of a histamine blocker to deal with ulcer disease. And, of course, now half the country is on proton pump inhibitors, and the highly selective vagotomy is in the Smithsonian Institution. No one does them anymore. You would have to go—it itself is a rare disease because you—no one has to have that anymore. It is hard to get the same, you know, to be able to account for the savings that Dr. Fordtran created with the development of his product, because all of the baby boomers who at that point were in medical school, but were on their way to developing ulcer disease, would have required that surgery at some point in their future.

Mr. NEIL. To say nothing of them cured of antibiotic therapy for helicobacter pylori, which——

Mr. BURGESS. Sure.

Mr. NEIL. Yes.

Mr. BURGESS. Thank you, Mr. Chairman. He—his gavel is the surrogate endpoint for my questioning.

Mr. PITTS. We will have a second round.

The Chair thanks the gentleman. Now recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman. And, again, thank our witnesses for your testimony today.

Without greater investment in antibiotics, we will face a future that resembles the days before these miracle drugs were developed,

one in which people died of common infections, and many medical advances that we take for granted today will become impossible, including surgery, chemotherapy and organ transplantation.

Dr. Neil, you mentioned in your statement, in 2012, PCAST recommended a limited population drug approval pathway in order to facilitate drug development. PCAST specifically identified antibiotics as an area where this pathway would be important, and as we know, the need for new antibiotics is urgent. The World Health Organization reiterated this just this month in a report of antibiotic resistance which said it is a very real potential for post-antibiotic era here in the near future.

My colleague, Dr. Gingrey, and I introduced the ADAPT Act which would create the pathway PCAST described. FDA officials from the Commissioner down have talked about the Agency's desire to work with Congress to get this done. We are eager for Congress to act quickly and given the urgency of the situation.

Dr. Neil, could you explain how this pathway would benefit antibiotic development?

Mr. NEIL. I think that—yes, it is on. I think it would benefit it tremendously, not only the development of it, but also the appropriate use of these new drugs once they get into clinical use. But the idea that one can identify very easily through surrogate markers the appropriate population with a serious infection, and be able to address that much more quickly, speed these antibiotics to the market, I think is a terrific one. And not only that, I think what we learn from this and how to implement it can be applied to other serious diseases later on, potentially.

Mr. GREEN. OK. Dr. Allen, cancer patients are particularly at risk for serious bacterial infections. Patients undergoing chemotherapy have suppressed immune systems, making it more difficult for them to fight off other diseases. Without antibiotics, chemotherapy would be significantly more dangerous.

Dr. Allen, you talk about a limited population pathway for antibiotics. Could—this could be important to cancer patients. Can you talk to us about that?

Mr. ALLEN. Sure. Well, as you mentioned, and thank you for your leadership in this area, risk of infection for cancer patients is certainly increased, and it has the potential to interrupt their treatment on a chemotherapy or other anticancer drug, that they may have to stop that treatment, and it could have a detrimental effect toward harnessing the growth of the cancer. Even more detrimentally is if a cancer patient who is immune-compromised is infected with microbial infection, it poses them at risk for serious adverse events and fatality. So it is not insignificant here both in the treatment of the cancer, but also in the survival of the patient.

Mr. GREEN. OK. In 1990, there were almost 20 pharmaceutical companies with large antibiotic research and development programs. Today, there are only two or three large companies with strong active programs, and only a small number of companies that have more limited programs.

Ms. Radcliffe, in your testimony, you mentioned that the ADAPT Act and the importance of the voluntary pathway that can help foster novel drug development. Can you elaborate on how this kind of pathway would address some of the economic challenges, particu-

larly the size, the cost and time it takes to complete clinical trials that may be hindering antibiotic—investment in antibiotics?

Ms. RADCLIFFE. Yes, certainly. BIO supports the ADAPT Act, and we thank you very much as well as Representative Gingrey for your work on developing this pathway. It has to walk a very fine line.

Mr. GREEN. Yes.

Ms. RADCLIFFE. It is important that sponsors be able to seek the designation early, or follow the pathway early on in development so that they can gain the benefits of being able to design a clinical pathway in a smaller population, and with attention from FDA as to the greatest clinical efficiency in those trials. This Bill would permit that to happen. It is also important that the pathway not infringe on the pathway—on the practice of medicine, and that is an important protection for patients. Physicians have to be able to use a product that they believe to be the best for their patient and the circumstances where the patient finds him or herself. And so, therefore, it is very important that such a pathway not infringe on the path—on the practice of medicine, and the Bill that you have introduced does that. So we think that it will be a very great—of very great assistance to sponsors in terms of incentivizing work in this incredibly important area for antibiotic resistance.

Mr. GREEN. Thank you, Mr. Chairman. I know I am out of time. To meet this crisis, we need a multi-prong approach that includes enhanced monitoring, better use of antibiotics, and investment in new therapies, and we can no longer ignore the risk of antibiotic resistance, the epidemic and the growing number of lives these superbugs claim.

And I thank you for having the hearing today.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. It is great to have you all here.

I have been interested, there is a Washington Post story published May 16 on the movement by States on right-to-try laws. The one column—part of the end of the article, and, Mr. Chairman, if we could submit it for the record. I——

Mr. PITTS. Without objection, so ordered.

[The information follows:]

The Washington Post

'Right to Try' laws spur debate over dying patients' access to experimental drugs

By Brady Dennis and Ariana Eunjung Cha, Published: May 16

Colorado, Missouri and Louisiana are poised to become the first states in the nation to give terminally ill patients the right to try experimental drugs without the blessing of the Food and Drug Administration, setting the stage for what could be a lengthy battle over who should decide whether a drug is too risky to try.

Lawmakers in the three states have passed "Right to Try" laws with unanimous votes in recent weeks, after high-profile, social media campaigns in which families of dying patients have pushed for access to unapproved but potentially lifesaving drugs. Colorado's governor is expected to sign that state's law Saturday.

Proponents of the measures argue that patients desperate for treatments must navigate a lengthy, cumbersome process to get the FDA to approve early access to experimental drugs and to persuade companies to provide them. The Right to Try laws are intended to cut through some of that red tape by essentially cutting the federal government out of the picture.

"For people who are facing death and have one last hope, they should have a choice to try every possible drug," said state Rep. Joann Ginal, a Democrat and co-sponsor of the bill in Colorado. Ginal introduced it in part because she witnessed how an experimental treatment helped her older brother, who has a rare blood cancer.

Opponents of the approach call it an ill-advised effort that circumvents federal law, undermines the drug development process and threatens to harm more people than it helps by providing access to medications that haven't been proven safe and effective.

"The notion is based on the 'Dallas Buyers Club' — the idea that you have to get around the indifferent and cruel government to get access to drugs," said Arthur Caplan, director of the bioethics division at New York University Langone Medical Center, referring to the Oscar-winning movie based on an AIDS patient who smuggled unapproved drugs into Texas during the 1980s.

The reality, Caplan said, is more complicated than singling out the FDA, which approves almost all the requests it receives for "compassionate use" exemptions. He noted that the new legislation does nothing to compel cooperation from drugmakers, who often are reluctant to hand out unapproved drugs, for reasons including high costs, lack of adequate supply and worries over liability.

Frank Burroughs, founder of the Virginia-based Abigail Alliance for Better Access to Experimental Drugs, which has long pushed the FDA to widen access, said people aren't after just any new medication that comes along.

"We're talking about 'promising' drugs," said Burroughs, whose group has helped the Goldwater Institute, a conservative advocacy organization, push for the state laws. "Patients are much smarter and savvy than they get credit for."

Burroughs said the FDA simply hasn't moved quickly enough and that people who are out of options are willing to take on more risk than an ordinary person. "The risk-benefit is much different than someone who's waiting for a new allergy medication or a new toe fungus cream," he said.

The FDA on Friday declined to take a position on any of the state Right to Try bills. But in a statement, the agency said it is concerned about any efforts that might undermine the "congressionally-mandated authority and agency mission to protect the public from therapies that are not safe and effective."

FDA regulations allow for access to investigational drugs outside of a clinical trial for patients who have serious or life-threatening illnesses and have no comparable alternatives. While these "compassionate use" exemptions can apply to individuals on a case-by-case basis, the FDA also can grant expanded access for larger groups of patients. However, the agency cannot force a company to provide a drug to patients.

The Right to Try bills aim to provide a streamlined alternative to the FDA process. Instead of having to fill out lengthy and complex paperwork, patients would only need to get an okay from a drug company and a simple prescription or "recommendation" from a doctor to access an unapproved treatment. The drugs involved also must have successfully completed an initial safety trial and moved to the next phase of development.

It's unclear how many drugmakers might be willing to make use of the state laws at the risk of angering federal regulators. But at least one company plans to take advantage of the new legislation in Colorado.

Neuralstem, based in Germantown, Md., has begun looking for doctors in the state to use its treatment — which involves surgically transplanting neural stem cells in the spinal cord — for Lou Gehrig's disease. The company's chief executive, I. Richard Garr, said results of its first trial, involving 15 patients, were promising in slowing down the disease's progression. "On average, these patients die within two to four years of diagnosis, so our hope is to make this available to everyone as quickly as possible," Garr said.

Sascha Haverfield, vice president of scientific and regulatory affairs at the Pharmaceutical Research and Manufacturers of America, said companies take expanded use requests seriously and evaluate each case carefully.

Ultimately, Haverfield said it's incumbent on all stakeholders — drugmakers, doctors, the FDA and patients — to figure out the most efficient way to get drugs to those who most need them. But he said it's also important not to undermine the clinical trial process, which can lead to FDA approval. Granting unwarranted expanded access requests not only places "an individual's health ahead of the public's health," he said, but it also could undermine the regulatory process and hinder a company's ability to make new drugs available to a broader patient population.

For Amy Auden, of Lone Tree, Colo., the decision to publicly push for the new law in her state was deeply personal. Her husband, Nick, died in November after a two-year battle with melanoma. For much of last year, the family tried unsuccessfully to persuade Bristol-Myers Squibb and Merck to give it access to a promising developmental drug for his cancer.

"Given that there was something on this earth to help Nick, we needed to do everything in our power to try to get it," said Auden, now a widowed mother of three. "Of course, there was a chance Nick would not have been in the 52 percent of people who are responding to the drug; however, a 52 percent chance at life is better than a zero percent chance at life."

With the new law, Auden said more families might at least have the hope that hers did not.

"Not a day goes by where it doesn't haunt me," Auden said. "Those with serious illnesses should not have to fight the illness as well as fight for the right to gain access to lifesaving treatments."

More from The Washington Post: Once in limbo, promising Duchenne muscular dystrophy drug back on track toward approval 'Mommy lobby' emerges as a powerful advocate for medical marijuana for children Girl at center of fight to legalize cannabis oil dies at age 7 Crowdsourcing medical decisions: The Josh Hardy case

Mr. SHIMKUS. There is a story about the spouse, Amy Auden, from Lone Tree, Colorado, who had—her husband had melanoma, 2-year battle, the last year they tried to get a promising drug, couldn't get it, and he has since passed. And her comment is, of course there was a chance Nick would have been in the 52 percent of the people who are responding to the drug, however, a 52 percent chance of life is better than a 0 percent chance of life, which was the dilemma that this family was placed in. And, hence, you see States moving to address this. It is not—what—a brief comment on this movement by States on—to right-to-try laws, and that is probably symptomatic of a slow process of getting drug therapies quickly to the market. Is that true? Let us just go from left to right, if you want? And if you don't want to answer, that is fine. I mean it is——

Mr. NEIL. Well, in my experience, FDA has always been very compliant in getting patients, you know, into small trials or compassionate use trials. To me, the issue has always been for smaller companies, having the resources to be able to provide that, and I think mechanisms——

Mr. SHIMKUS. This wasn't a small company that she had to deal with——

Mr. NEIL. Yes.

Mr. SHIMKUS [continuing]. So——

Mr. NEIL. Well, yes, I think that there should be some way for companies to recover their cost, and to get patients into trials, and to be able to collect the information that you need to make that——

Mr. SHIMKUS. Right.

Mr. NEIL [continuing]. Usable.

Mr. SHIMKUS. And please kind of go quickly. I have got—actually my two official questions that I need to get to.

Ms. RADCLIFFE. So this is a very, very difficult issue. BIO has a board-level Biothics Committee which is currently involved in taking a deep look at the issues around expanded access. I think everyone understands that if somebody in their own family were in such a situation that they needed an investigational product, I think most of us would do everything that we could to——

Ms. SHIMKUS. But is the statement——

Ms. RADCLIFFE [continuing]. Ensure——

Mr. SHIMKUS [continuing]. About the process——

Ms. RADCLIFFE. Yes.

Mr. SHIMKUS [continuing]. And how slow and methodical, and people who—it is happening, I mean these are—there are three States I think, there is Colorado, one is going to be signed into law on Saturday, from what I am reading, and that is a response to people feel that they are not getting a chance to fight for their life, and they are being held up either in the—let me move forward. I—because I need to move on on these two other questions. On the presence counsel raises the fact that in recent years there has been a regulatory uncertainty about a variety of important issues that has hindered investment and innovation. One such issue is combination of therapies and studies that are required for their approval.

Has FDA since provided sufficient clarity in this area, or is there need to ensure greater regulatory certainty for companies to spur

further innovation in this increasingly important area of drug development? Anyone want to try it?

Mr. NEIL. I think there is further need, particularly outside of cancer, to echo Mr. Sasinowski's comments earlier.

Mr. SHIMKUS. Great, thank you. Anyone else?

Mr. TUNIS. Yes, you know, and I would just add again, sort of related to some of the comments I made in my testimony, that the better equipped, you know, we are in the context of delivering healthcare to get the additional information about, you know, products that are approved through an accelerated pathway, I think the more the FDA can count on some of the unanswered questions about safety, you know, safety and effectiveness to be efficient—to be answered at least at some point, and then the opportunity to accelerate—to use the accelerated authorities more frequently, I think, is enhanced as the delivery system gets better at filling in what is not studied pre-market.

Mr. SHIMKUS. Let me finish with this last question, and the rest I will submit for the record.

A second distinct area that report highlights which is of particular interest to me is the issue surrounding the certainty and the regulatory pathway when it comes to therapies for which patients are picked based upon companion diagnostics. The companion diagnostic may or may not be approved already, adding an additional layer of complexity for the sponsor.

Do any of you witnesses have experience in this area to comment on what needs to be done to encourage investment and innovation for these personalized approaches?

Mr. ALLEN. So the trial that I mentioned with regards to lung cancer is working to try and advance these technologies through the regulatory process, by using new technologies that have the ability within a single test to monitor the activity and presence of different genetic alterations. So it has the ability to really reform the current single test paradigm with a single drug. But I think the FDA has been proactive in issuing guidance documents both from the drug and diagnostic side, to begin to lay out what their feelings are on how to generate this evidence, but some of this is also an artifact of making sure that there is a robust research enterprise to really understand which are those true alterations that are driving different diseases.

Mr. SHIMKUS. Great, thank you.

My time has expired. Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman.

The PCAST report's fourth recommendation is the creation of a new pathway that manufacturers could choose to use for initial approval of drugs shown to be safe and effective in a specific subgroup of patients. The report notes that such approvals could sometimes be based on relatively small and rapid clinical trials showing a favorable safety and effectiveness risk benefit ratio for the narrow population most in need of the drug, however, it notes that for such a pathway to work, FDA would have to be confident that the

drug generally would not be used beyond the limited population for which it was evaluated and intended.

Dr. Allen, do you think the pathway makes sense if FDA does not have adequate authority to ensure that the designation is used to inform potential users and payers of the special standing and circumstances surrounding approval of the drug?

Mr. ALLEN. I think it is important to state that the intention of the limited population pathway is to still operate within the confines of safety and efficacy, and that is not altered. I think that ensuring appropriate use of these types of products will require a great deal of interaction with the medical community, and make sure—in making sure that the appropriate lines of communications are present, to make sure that the benefit risk profile within that subset is maintained, and communicating clearly that the benefit risk for the entirety of the population may not be known yet, but those patients with the most life-threatening version of that disease don't have the time to wait. So this allows for access for those with the most severe form of a relatively common illness.

Mr. WAXMAN. So you think that if a—if they have adequate authority to designate this information, that that would be important if they are going to release this drug before it is approved for the general population?

Mr. ALLEN. Yes, certainly, and having the ability to communicate is largely based on the label, as it is with all prescription drugs——

Mr. WAXMAN. Um-hum.

Mr. ALLEN [continuing]. But in this case, it would be important to indicate if there is—if this has only been tested in the most severely ill patients, through use of some sort of symbol——

Mr. WAXMAN. Um-hum.

Mr. ALLEN [continuing]. Or logo to communicate it, but also the ability to pre-review marketing material, and that has been an effective strategy in other areas such as accelerated approval.

Mr. WAXMAN. Let me turn to another recommendation in the report. Recommendation five has to do with another new potential mechanism for more quickly making new therapies available to patients, a so-called adaptive approval. As I understand it, adaptive approval refers to the concept that there would be a series of approval stages that would gradually allow a new therapy to be marketed for broader patient population, so as more is learned about a drug, the use of it could be expanded.

The PCAST apparently explored this concept extensively, however, in its final recommendation, it said that Congress should not legislate this new pathway, instead, any use of this approach should instead be tested in pilot projects.

Dr. Allen, can you say more about why PCAST was hesitant to have any legislation on this pathway at this point?

Mr. ALLEN. Well, I don't want to speak on behalf of the entire work group, but, you know, from my perspective, it is very difficult to have one set of rules that governs a very diverse set of products——

Mr. WAXMAN. Um-hum.

Mr. ALLEN [continuing]. And given the pace at which science is accelerating, I think many of the other witnesses on the panel today have talked about some really innovative approaches to dif-

ferent diseases, and it is hard to really kind of draw a single line in the sand. A drug for prevention is very different than a drug for late-stage pancreatic cancer, and the benefit risk profile of that is very different——

Mr. WAXMAN. Um-hum.

Mr. ALLEN [continuing]. And so it is hard to codify that into law.

Mr. WAXMAN. Mr. Sasinowski, do you have anything to add on this? Why did PCAST recommend against legislation?

Mr. SASINOWSKI. I cannot speak for PCAST, just as Mr. Allen can't, but for my own perspective, and that from NORD, is our perspective is that it was premature. It merits exploration, but at this time, you know, trying to integrate that and come up with a system, we didn't have a program in front of us that had enough granularity for us to speak to it with any confidence. So I think that this is in the exploratory world.

Mr. WAXMAN. And I appreciate that.

Let me, Mr. Chairman, just briefly mention one other critical issue that deserves a hearing in and of itself. We need new therapies to be marketed but we have got to address high prices for these therapies. They are no good for anyone if we can't afford them. And I have a recent article from the New York Times that describes the hardships faced by patients with chronic diseases who can't afford the price of their treatments. It notes that the high prices of treatments for diabetes and other chronic diseases are a major contributor to the U.S.'s $2.7 trillion annual health bill. This is an issue we will have to address at some point. And I would ask unanimous consent this article be made part of the record.

Mr. PITTS. Without objection, so ordered.

[The information follows:]

The New York Times http://nyti.ms/PxdJNO

Even Small Medical Advances Can Mean Big Jumps in Bills

By ELISABETH ROSENTHAL APRIL 5, 2014

MEMPHIS — Catherine Hayley is saving up for an important purchase: an updated version of the tiny digital pump at her waist that delivers lifesaving insulin under her skin.

Such devices, which tailor insulin dosing more precisely to the body's needs, have transformed the lives of people with Type 1 diabetes like Ms. Hayley. But as diabetics live longer, healthier lives and worries fade about dreaded complications like heart attacks, kidney failure, amputations and blindness, they have been replaced by another preoccupation: soaring treatment costs.

"It looks like a beeper," said Ms. Hayley, a 36-year-old manager here for an environmental services company, referring to the vintage 2007 pump on the waistband of her jeans. "It's made of plastic and runs on triple-A batteries, but it's the most expensive thing I own, aside from my house."

A new model, along with related treatment supplies, prices out at tens of thousands of dollars for this year and will cost her about $5,000, even with top-notch insurance. "It's great," Ms. Hayley said, "but it all adds up."

Traditionally, insurers lost money by covering people with chronic illnesses, because they often ended up hospitalized with myriad complications as their diseases progressed. Today, the routine care costs of many chronic illnesses eclipse that of acute care because new treatments that keep patients well have become a multibillion-dollar business opportunity for device and drug makers and medical providers.

The high price of new treatments for diabetes, rheumatoid arthritis, colitis

and other chronic diseases contribute mightily to the United States' $2.7 trillion annual health care bill.

More than 1.5 million Americans have Type 1 diabetes and cannot survive without frequent insulin doses, so they are utterly dependent on a small number of producers of supplies and drugs, which have great leeway to set prices. (Patients with the far more common Type 2 diabetes — linked to obesity — still produce insulin and can improve with lifestyle changes and weight loss, or on oral medicines.)

That captive audience of Type 1 diabetics has spawned lines of high-priced gadgets and disposable accouterments, borrowing business models from technology companies like Apple: Each pump and monitor requires the separate purchase of an array of items that are often brand and model specific.

A steady stream of new models and updates often offer dubious improvement: colored pumps; talking, bilingual meters; sensors reporting minute-by-minute sugar readouts. Ms. Hayley's new pump will cost $7,350 (she will pay $2,500 under the terms of her insurance). But she will also need to pay her part for supplies, including $100 monitor probes that must be replaced every week, disposable tubing that she must change every three days and 10 or so test strips every day.

That does not even include insulin, which has been produced with genetic engineering and protected by patents, so that a medicine that cost a few dollars when Ms. Hayley was a child now often sells for more than $200 a vial, meaning some patients must pay more than $4,000 a year. Other refinements have benefited a minority of patients but raised prices for all. There are no generics in the United States.

Companies that produce the treatments say the higher costs reflect medical advances and the need to recoup money spent on research. But David Kliff, a financial analyst who is editor of Diabetic Investor, an independent newsletter on the industry, points out: "Diabetes is not just a disease state; it's a huge business, too."

Those companies spend millions of dollars recruiting patients at health fairs, through physicians' offices and with aggressive advertising — often urging them to get devices and treatments that are not necessary, doctors say. "They may be better in some abstract sense, but the clinical relevance is minor," said Dr. Joel

Zonszein, director of the Clinical Diabetes Center at Montefiore Medical Center.

"People don't need a meter that talks to them," he added. "There's an incredible waste of money."

Even patients with insurance often feel squeezed by large out-of-pocket costs, and many describe holding old pumps together with duct tape, rationing their test strips and skimping on insulin. Dr. Jeoffry B. Gordon, a family practitioner in San Diego, said he had patients with failing kidneys and others who had ended up in emergency rooms because they could not afford their maintenance care.

"From a guy on the front lines, the improvements have been miraculous," he said. "But the acquisition cost is very high, and the pricing dictates what treatment you get."

Complication rates from diabetes in the United States are generally higher than in other developed countries. That is true even though the United States spends more per patient and per capita treating diabetes than elsewhere, said Ping Zhang, an economist at the Centers for Disease Control and Prevention.

The high costs are taking their toll on public coffers, since 62 percent of that treatment money comes from government insurers. The cumulative outlays for treating Type 1 and Type 2 diabetes reached nearly $200 billion in 2012, or about 7 percent of America's health care bill.

Expenditures could well double by 2030, according to estimates by the C.D.C., in large part because the number of Americans found to have diabetes has been increasing more than 50 percent every 10 years. Most of the increase is attributable to Type 2 diabetes patients, whom manufacturers are encouraging to try insulin treatment and glucose monitoring, even though that is rarely medically required. Also, the Affordable Care Act requires health insurers to cover people with chronic disease, meaning they will have better access to treatments.

"This is not just a health care crisis," said Mr. Kliff, the newsletter editor, who has Type 1 diabetes. "It's an economic crisis as well."

Maintaining Control

Catherine Hayley was born in 1977, the year before the first synthetic human

insulin was made using new gene-splicing technology. Her diabetes was diagnosed when she was 9, about the time this new generation of genetically engineered insulin was brought to market. One of her earliest memories is practicing insulin injections on an orange.

The development of insulin therapy in the 1920s was one of the great medical triumphs of the 20th century, on a par with the discovery of antibiotics. Before then, Type 1 diabetics often died within a year and were on such restrictive diets that they sometimes succumbed to starvation.

Diabetes is an autoimmune disease in which the pancreas stops producing the hormone insulin. Without it, sugars build up in the blood, producing symptoms like blurry vision, exhaustion and frequent urination and leading to a severe accumulation of acids that can be rapidly fatal. Even when treated with insulin shots, moderately high sugar levels over the long term can damage the eyes, heart, kidneys and nerves. But if too much insulin is given, blood sugar can plummet, leading to unconsciousness and seizures. Because digestive enzymes degrade insulin, it cannot be swallowed, and must be injected.

When Ms. Hayley's diabetes was diagnosed, maintaining that balance involved testing a drop of blood on a paper strip that would change color to indicate — within a wide range — the patient's glucose level. Patients would typically give themselves a shot of insulin morning and night in response to the results.

"What I ate was all very regimented, and it had to be at the same time each day," she recalled. At school every day at 10 a.m., she pulled out a snack of a precisely weighed chunk of cheese and rice cakes.

The treatment tools were initially cheap: simple syringes and pig insulin, which is almost identical to that made by the human body. But that all changed after a landmark study in 1992 showed that patients did better if they maintained very tight control — keeping their blood sugar within a nearly normal range by checking it frequently and taking multiple insulin shots a day. Around the same time the business of American medicine was changing, too, with direct-to-consumer advertising, proprietary treatments and designer insulin in development.

When Ms. Hayley left Memphis for Colorado College in 1996, she was using a tiny meter through which she could get more precise measures of her blood sugar

level, a penlike injector containing insulin with an adjustable dose, and human insulin made with gene-splicing technology. All were covered by patents.

She did not switch to a pump until 2006 when, after years of waiting tables and studying in graduate school, she got her first job with insurance benefits. "It controls my blood sugar better," she said, on her way to a dinner that included sharing a once-forbidden fruit cobbler. "I'm really able to live how I want. However, the price has increased dramatically."

The tiny squirts from her pump are delivered more precisely by patented systems with microchip sensors and Bluetooth capability, with technical support by company representatives in endocrinologists' offices. When Ms. Hayley pricks her finger, it is with a customized lancet to go with a customized test strip that fits into a customized meter, which transmits the result wirelessly to her compatible insulin pump, which delivers the appropriate insulin dose. (There is not yet a one-device-does-all that automatically performs the pricking, measuring and dosing.)

While some components, like the meters, are low cost or even free for patients, their supplies are costly. Dr. Spencer Owades, a dentist in suburban Denver with Type 1 diabetes, said he was shocked to discover that his test strips — which cost just pennies to make — were priced at $1.50 apiece when he ran out and had to buy them at a pharmacy. He usually received them in the mail through his insurer and uses five to 10 a day.

"It's a printer model," he said, "where the printer is cheap, but they get you on the cartridges." He added: "But if you have diabetes, they have you over a barrel."

Planned Obsolescence

Diabetes experts say a good part of what companies label as innovation amounts to planned obsolescence. Just as Apple customers can no longer buy an iPhone 3 even if they were content with it, diabetics are nudged to keep up with the latest model.

Medtronic is the dominant insulin pump manufacturer, serving 65 percent of American patients and the majority of those worldwide. Though smaller companies sell cheaper pumps, it is hard to make inroads: Once familiar with the

Medtronic system and its extensive support network for troubleshooting problems, patients are reluctant to switch. Doctors are leery of prescribing equipment from a new company that may be out of business in a year; their office computer may not sync with the new software anyway.

Medtronic declined to talk about specific prices, but said a core tenet was to make only "a fair profit." Amanda Sheldon, a spokeswoman, added: "We are committed to reinvesting in research and development of new technologies to improve the lives of people with diabetes, and our current pricing structure ensures that we can bring new products to market."

For the small meters to test blood sugar, "the technology isn't very sophisticated — it essentially hasn't really changed much in the past 25 years," said Dr. John Pickup, a professor of diabetes and metabolism at King's College London. "The test strips are based on an electrochemical reaction. The new meters are a bit more sophisticated — they can make charts and things like that. It's a little bit of added value to the patient. But the companies can charge a lot more money."

The types of insulin available have evolved as well, as has their price. Synthetic human insulin is safer for patients, who sometimes developed reactions to animal insulin. But it is made by only three companies: Eli Lilly, Sanofi and Novo Nordisk. Manufactured in microbes, each one's product has minor dissimilarities that reflect the type of cell in which it was made. Since the companies owned the cell lines, it is nearly impossible for other companies to make exact copies or even similar versions that would be cheaper, even once the patents expire. And the pharmaceutical companies defend the patents ferociously.

What's more, the three companies continued to refine their product, adding chemical groups that made the insulin absorb somewhat more quickly or evenly, for example. They are called insulin analogues, and their benefits are promoted tirelessly to doctors and patients.

"The insulins are tweaked for minor benefits that may help a small number of patients with difficult-to-control diabetes, and result in major price increases for all," Dr. Pickup said. Because of analogues, he added, Britain's National Health Service has had to spend 130 percent more on insulin in the past five years.

In the United States, said Dr. Zonszein at Montefiore, the price of Humalog, Lilly's analogue insulin, was typically two to four times that of its older human

insulin line, called Humulin. "There is not a lot of difference between Humulin and analogues," he said, but he noted that Humulin was getting "hard to find." Sanofi Aventis has stopped selling its older product in the United States, and Mr. Kliff, the financial analyst, said other companies were likely to follow suit, effectively forcing patients to use the costlier versions.

Dr. Todd Hobbs, chief medical officer of Novo Nordisk, defended the rising prices of insulin, linking them to medical benefits. "The cost to develop these new insulin products has been enormous, and the cost of the insulin to the consumer in developed countries has risen to enable these and future advancements to occur," he wrote in an email.

Patients get squeezed between insurers or employers, who are trying to limit their outlays, and the suppliers. The constant shifts in products and prices are a challenge for even the most sophisticated consumers.

Denise Lombard, an insurance broker in Oakland, Calif., whose 16-year-old daughter, Gabrielle Woodland, has diabetes, said many policies contained "not one word about how they are going to cover insulin and supplies." Gabrielle's current policy does not cover glucagon, a hormone injection — which retails at $272.72 a dose — that families of diabetic children are told to stock should they faint because their blood sugar drops too low.

Jonathan Lloyd, a pharmacist in upstate New York, has been frustrated trying to manage the care of his daughter, Erin, 25, who uses a pump with a built-in glucose meter and is teaching in Nicaragua. When Mr. Lloyd went to fill the four prescriptions for her supplies this year, he discovered many of them were no longer covered by his insurer, which had switched to reimburse a different brand of insulin and a different metering system, because the insurer got a better deal.

He now faces a dilemma: His daughter could switch to the new type of meter, which cannot communicate with her pump, which would mean her current meter would sit uselessly on her waist. Or he can pay thousands of dollars to buy supplies for the meter she already has. "It's so complicated — there are all these hidden costs, and I'm a pharmacist, for crying out loud," he said.

Meanwhile, as the price of supplies rises, endocrinologists remain among the lowest-paid specialists in American medicine, meaning severe physician shortages in many areas and long waits to see a doctor.

Chronic Diseases

Most other developed countries — with or without national health systems — provide free care and supplies for people with chronic diseases, reasoning that the disease is a natural catastrophe that fells its victims unpredictably. Also, with such policies in place, other countries and health care systems bargain hard with drug and device makers to bring down list prices.

In Germany, where everyone must have private insurance and contribute co-pays, people with diabetes get their care free; the price of pumps and insulin is negotiated by the government. In Britain, each hospital negotiates for pumps for its patients, getting prices that are typically less than half those in the United States, Dr. Pickup said. The vial of insulin analogue that Ms. Hayley gets for $200 at an American pharmacy is typically bought by British pharmacists for under $30 and dispensed free.

Some economists say manufacturers extract high prices in the United States to compensate for the fact that national purchasers overseas demand bargains. That may be justified in a world where bringing a new drug to market can cost $1 billion, they add.

"To some extent, Europe is getting a free ride from the U.S.," said Robert J. Shapiro, an economist and chairman of Sonecom L.L.C., a Washington-based financial advisory firm. "Drugs and equipment makers operate in a global market, and our costs are higher because every other country applies price controls, and we don't."

Mr. Kliff, the financial analyst, said some companies were no longer willing to sell in Germany as ever-tougher price negotiations have eaten into their margins. "I'm not saying they can't make money there — they can," he said. "But they can't make the kind of money they make in the U.S." He added that diabetes treatments remained highly profitable in the United States; insulin, for example, yields profit margins of around 70 percent.

With growing frustration but limited tools, the federal government has taken some tentative steps to fight back. Medicare is not allowed to bargain for insulin

prices. But for the first time last year it instituted competitive bidding for diabetes supplies, cutting reimbursements for test strips, for example, by about 60 percent.

Even when governments negotiate prices and foot the bill, patients may feel the rising price of diabetes care in other ways: While about one-third of Type 1 diabetics use pumps in the United States, that number is under 10 percent in Britain. What is the right number? Since pumps are complicated to operate, young children cannot use them, and some patients prefer syringes that operate like pens because they do not like having pumps attached.

The British government will not dispense these costly items unless a patient's diabetes has proved uncontrollable using other methods, but many doctors feel the devices are underutilized in Britain.

In the United States, each patient with a chronic disease must make the cost-benefit analysis of each new high-priced treatment, weighing symptoms, disposable income and insurance coverage. They are often wrenching decisions.

For Kristen Bailey, 28, of Colorado Springs, who has Crohn's disease, an intestinal disorder, that meant not marrying her fiancée so she could continue to qualify for drug company assistance programs that provide, at no cost, two medicines with list prices of more than $16,000 a year in the United States.

For Jeffrey Kivi, 51, a chemistry teacher at Stuyvesant High School in New York, it meant recently giving up an intravenous drug that, as an outpatient, he had had infused every six weeks for years to keep his psoriatic arthritis at bay. Before taking that drug, Remicade, Dr. Kivi was on high doses of steroids for debilitating joint pain that left him unable to walk at times.

But when his last three-hour infusion at NYU Langone Medical Center's outpatient clinic generated a bill of $133,000 — and his insurer paid $99,593 — Dr. Kivi was so outraged that he decided to risk switching to another drug that he could inject by himself at home. That is true even though his insurer did not require him to make up the difference.

"I cannot, in good conscience, continue to force my insurance company to pay $100,000 to NYU each time I get a Remicade infusion," Dr. Kivi, who was a drug company researcher for many years, wrote to the hospital. "That's insane."

In a statement, Lisa Greiner, a spokeswoman for the medical center, said Dr. Kivi's charge had been high relative to that of other patients because he had been prescribed a high dose of the drug.

He had moved his care to NYU Langone to follow his longtime doctor, who had moved her practice from a nearby hospital where the same infusion had been billed at $19,000. The average price that hospitals paid for Dr. Kivi's dose of Remicade late last year was about $1,200, according to Medicare data.

Changing drugs is not an option for patients with Type 1 diabetes, like Ms. Hayley. They need insulin.

She is resigned to paying her share of the new Medtronic insulin pump. And she is steeling herself for other new costs that will bring. The pumps are designed to work with yet another new device called a continuous glucose monitor — bought separately — that could be lifesaving for some patients with unstable diabetes, because it sounds an alarm and suspends insulin flow if it detects that blood sugar has dropped dangerously low, which can happen during sleep.

This device has two parts: a disposable probe, which is attached to the body and measures the glucose level in the skin, and a transmitter that attaches to the probe to calculate the results and send to the pump. The probes retail for over $100 and must be changed every six days; the transmitter costs about $600. (Since such devices are not precise enough to adjust insulin doses — they are meant primarily to detect trends — Ms. Hayley will have to continue pricking her finger for meter measurements as well.)

She does not yet know how well her insurer will cover those. "You want me to be able to afford good treatment," she said. "Because otherwise I end up disabled."

Correction: April 13, 2014

An article last Sunday about the rising costs associated with the routine treatment of many chronic illnesses described incorrectly glucagon, a drug that families of diabetic children are advised to keep on hand. It is a hormone injection, not an injection of concentrated sugar water. And a caption with an accompanying chart described incorrectly a picture of medical supplies one patient uses to treat her diabetes. It is an emergency glucagon kit, not an emergency insulin kit.

Follow Ms. Rosenthal on Twitter.

A version of this article appears in print on April 6, 2014, on page A1 of the New York edition with the headline: Even Small Medical Advances Can Mean Big Jumps in Bills.

Mr. WAXMAN. Thank you.

Mr. PITTS. The Chair thanks the gentleman.

And now recognize the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman. And good morning to you all.

The State I represent, New Jersey, represented as well by Ranking Member Pallone, is certainly among the medicine chests of the world, and a center of significant biomedical innovation. We are the proud home to tens of thousands of jobs in these life-saving industries. These companies reinvest hundreds of millions of dollars each year back into R&D in order to bring much-needed therapies to patients, to market.

I am deeply concerned about the slashing of R&D budgets that may look good on a financial spreadsheet, but I think would be tragic for patients moving forward. I ask this out of a concern regarding recent news on certain potential acquiring companies' intentions to slash R&D spending, for example, in the case of Allergan, a company that provides hundreds of jobs in the congressional district I serve. A potential buyer of Allergan has stated that it can achieve cost synergies by cutting approximately $1 billion in investment in R&D, and eliminate 5,000 high-quality U.S. jobs, as well as lower its tax rate from 26 percent to low single digits. Companies like Allergan invest significant capital in R&D in order to continue to development treatments for unmet medical needs. These investments not only support high-skilled, well-paying jobs, but also continue to deliver new, potentially life-saving products in the development pipeline. I am concerned that this could become the model for other such mergers, and we would lose the engine for innovation and growth here in the United States.

To you, Ms. Radcliffe, how dependent are future cures on robust commitments in the private sector to research and development?

Ms. RADCLIFFE. Thank you. So BIO is unable to comment on any particular companies——

Mr. LANCE. Yes, I realize that but——

Ms. RADCLIFFE [continuing]. Businesses and things——

Mr. LANCE [continuing]. In general, please.

Ms. RADCLIFFE. We are not familiar with that. I personally am not familiar with the situation, specifically in the case that you mentioned, to make any comment whatsoever. Obviously, the mission of BIO is to ensure that there is a research—a robust research and development pipeline in the United States for the development of new cures that will help patients and meet unmet medical needs.

Mr. LANCE. And do you believe that the level of research and development now in this country, in private companies, that, in general, that is the level that should continue and perhaps even increase?

Ms. RADCLIFFE. Again, not commenting on any specific company, because there—every individual company may have its own situation with respect to exactly the level of research and development that it is conducting, as opposed to research and development that it licenses in or that are conducted in partnerships and so forth, however, I think that it—for BIO, again, the level of research and

development in the United States is extremely important, as I said in my testimony, it is very important that we as a Nation continue to elevate our research and development for the purposes of meeting unmet medical needs for patients, and also in terms of global competitiveness.

Mr. LANCE. So in general, you favor more research development funding as opposed to fewer funds in that portion of the larger whole?

Ms. RADCLIFFE. As a general principle, yes.

Mr. LANCE. Yes.

Ms. RADCLIFFE. And, of course, it would matter as to how that research and development funding were specifically spent.

Mr. LANCE. Thank you.

To the panel in general, the President's Council of Advisors on Science and Technology states that one of the most powerful incentives for drug development is granting periods of exclusivity to new drugs. It also mentions the economic disincentives created by long clinical trials required for conditions such as Alzheimer's Disease. The President's council acknowledges that engaging in the economic analyses required to provide potential policy changes is beyond the scope of the report and outside core experience. That being said, Hatch-Waxman was enacted in 1984, and it is indisputable that the time and cost it takes to develop a drug has significantly increased over the course of the last 3 decades. There are many potential therapies that would address other unmet medical needs, such as rare diseases and mental health, areas in which I am involved; I am the Republican chair of the Rare Disease Caucus, that lack sufficient patent protection.

To the panel in general, what are your thoughts on using data exclusivity to address these issues?

Mr. SASINOWSKI. You know, first, on behalf of NORD, I want to acknowledge Congressman Lance's leadership in the congressional caucus on rare diseases.

Mr. LANCE. Thank you very much.

Mr. SASINOWSKI. We have so awarded you, you know, on behalf of your leadership in that area, and we believe that the ability of all—let us say the Orphan Drug Exclusivity Act had a tremendous incentive that has sparked a great deal of research and development for rare diseases. You heard even Dr. Neil mention that his company is moving in the area of rare diseases, maybe in part because of the economic incentive that is provided by the Orphan Drug Act. So these kind of incentives have been powerful. Every person or every organization that has examined it has found their utility. The question though that is sometimes raised, Congressman Lance, is should we, for instance, expand the exclusivity, should we enter into the orphan drug exclusivity now that we have other forms of protections that exceed 7 years, perhaps in order to re-establish the primacy of orphan drug exclusivity that should be extended beyond 7 years. So these questions have been raised, and they are serious questions that I think that merit further discussion.

Mr. LANCE. Thank you.

I yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentleman from Virginia, Mr. Griffith, 5 minutes for questions.

Mr. GRIFFITH. Mr. Allen, you indicated it is hard to legislate or to come up with a good legislative model when you have all these different diseases, and you have some which are fatal and quickly fatal, others which are chronic. Don't you think simpler might be better, and that maybe Mr. Sasinowski's chart might be of some help in that regard?

Mr. ALLEN. Absolutely, and I think that was what was intended and what the committee enacted through the breakthrough therapies designation; a very simple requirement of early clinical activities showing a substantial improvement that results in a very flexible, intensive collaboration to get that drug through the process.

Mr. GRIFFITH. And sometimes we get fancy. We like to do things that are more complicated.

Mr. Sasinowski, you want to talk about your chart again for a minute? Somebody might not have been watching earlier.

Mr. SASINOWSKI. Well, thank you, Congressman Griffith. As a fellow Virginian, I appreciate that.

I am holding up a paperclip. Sometimes a paperclip can do an awful lot of good. And so I have been involved in this area of drug innovation, like I said, for more than 3 decades, and I have wrestled with this question of what can we do as—to achieve what we all want to achieve, like to accelerate approvals. And when I have been involved in this process, I see how often, shockingly, these very simple concepts that the Congress has created, such as fast track, you know, are not considered, and if we just give them more visibility, it sounds so simple, but if we required that at every new therapy that were to come before the FDA, there would be a simple question put, is this therapy one that would be a candidate for accelerated approval, it wouldn't take hardly any resources to consider that, it wouldn't delay at all the review of it, but it might spark the very kind of thing that others around the table here have talked to, that if we are going to engage in accelerated approval, we have to start that engagement early in order to identify intermediate clinical endpoints, and identify surrogates that can be used. And so since we are not recognizing the utility of it until, at all, very late in the process, we lose that—we forfeit that opportunity.

So thank you, Congressman, for recognizing that.

Mr. GRIFFITH. All right, I appreciate that. I would ask you to put on your thinking caps. I don't necessarily expect an answer today, but if you can think of what other legal barriers are out there that are currently limiting the potential for doctors, researchers, drug companies, to communicate on how therapies are working for patients in the real world, and what can we do to break down some of those legal barriers that are preventing reasonable and valuable treatments from getting to the patients. And if you have an answer today, I would be glad to hear it. Got about 2 minutes of my time left, if you want to use it. If not, if you could submit ideas for the record, I would greatly appreciate that.

Mr. SASINOWSKI. Well, Congressman——

Mr. GRIFFITH. Yes, sir?

Mr. SASINOWSKI [continuing]. One thing I am not sure about the legal—even though I am a lawyer, I am not sure about the legal impediment. I will have to think about this further, but many of the members of this committee have suggested issues that where natural histories or registries could be a very valuable tool. If we understood more about the natural history, progression of a disease, we could better understand how it might work in a small population. We could be able to discern what is the treatment benefit, versus what is the natural course of disease, and in the same way, we can tell, separate what is a safety signal that is a true safety signal that might be due to the therapy, from just a signal that is part of the natural course of the progression of the disease.

So these natural histories and registries are very important. We, on behalf of NORD, have been encouraging the development of them in every area, and there are difficulties in trying to get physicians and trying to get medical institutions to be able to share information, and to be able to have uniform information so that we are not talking about apples and oranges. We need some sort of common lexicon in these areas.

So I don't have the specific answer of what are the legal aspects of that——

Mr. GRIFFITH. Right.

Mr. SASINOWSKI [continuing]. But I know what the target should be.

Mr. GRIFFITH. I appreciate that.

Mr. Chairman, if anyone would like my time. If not, I yield back.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentlelady from North Carolina, Mrs. Ellmers, 5 minutes for questions.

Mrs. ELLMERS. Thank you, Mr. Chairman, and thank you to our panel for being here today on this very important issue.

I represent the Second District of North Carolina, and in our district we have 70,000 veterans, and I am very proud to represent them. Many of them are returning home from Afghanistan, and certainly have come home from Iraq, and are living in our communities with PTSD, and I know that is something that you are all aware of. I understand that new path-breaking technologies are emerging in treating veterans with PTSD, specifically, the use of magnetic resonance therapy.

Dr. Neil, this is a question for you: Do you know if the Department of Veterans Affairs has looked into any of these new technologies, in particular, into the magnetic resonance therapy treatment?

Mr. NEIL. Thanks, Mrs. Ellmers. No, I do not know that.

Mrs. ELLMERS. OK. Getting into the issue of how we need to move forward on many of these treatments, such as PTSD. You know, there is broad agreement that the present system that we have with clinical trials is ineffective and costly. There was an expert that participated in the PCAST report that estimated a more efficient clinical trial system could cut the cost in half across the industry.

Dr. Neil, do you have any thoughts on what we can do to make trials more efficient and less expensive, and what would this mean to the R&D budgets across the industry?

Mr. NEIL. Well, thank you again. First of all, I would just say that it would have a huge impact because more than 40 percent of industrial R&D expenditure is in the area of clinical trials.

Mrs. ELLMERS. Um-hum.

Mr. NEIL. And one of the reasons that we formed TranCelerate Biomedical as an industry collaboration was to address clinical trials' inefficiency, and there, we looked at this and said these are areas where we do not have, cannot really realize any competitive advantage, and we are all spending the same money over and over again to basically reconstruct a clinical trial's——

Mrs. ELLMERS. Um-hum.

Mr. NEIL [continuing]. Infrastructure every time. We are all using the same investigators, we are all training the investigators, and then we are not recognizing each other's training. We all have our own Web site to communicate with—so on and so forth. And so we took that on, and the early results are very promising as a way to be able to increase a lot of efficiency, reduce the burden on clinical investigators——

Mrs. ELLMERS. Um-hum.

Mr. NEIL [continuing]. And reduce the cost. I think there are a lot of other great examples, the cystic fibrosis example being one of them, with their clinical trials network where specific—or disease-specific networks could be created, so you become plug-and-play by being able to start these trials very quickly, and this new lung cancer master protocol, I think, is a great innovation in that direction.

So taken all together, I believe there is an enormous amount of efficiency on the table. There are a lot of things in my testimony that I specifically recommended around IRB's, safety monitoring boards, clinical trial networks, and new innovative approaches to this like, again, in your State, the Duke Clinical Research Institute, their collaboration with the NIH——

Mrs. ELLMERS. Um-hum.

Mr. NEIL [continuing]. With the collaboratory. So they are exploring ways to be able to randomize using electronic health records and test different therapies. I think we need to explore all of that, and there is no doubt that we will have the greatest impact on accelerating these cures to patients, reducing costs, and making the whole system work better if we could take that on. And I think Congress could do a lot here.

Mrs. ELLMERS. Thank you, Dr. Neil.

Let me see, time. About a minute left.

Dr. Tunis, I have a question, and it gets back to the issue that has been asked a number of times on how much of the patient involvement is taken into account, especially in the FDA, when it comes to moving forward in an accelerated fashion. How does the FDA view the patient input on some of these issues?

Mr. TUNIS. Certainly aware that there is a, you know, a couple of focused initiatives going on at the FDA that are really trying to enhance the degree to which patient perspectives are taken into account. There is the patient focus drug development that I believe came out of the FDAMA was—and FDASIA was—OK. And then on—in the—actually, in the Center for Devices, there is a medical device innovation collaborative that is very much focusing on pa-

tient perspectives on benefit risk, very much with the notion that, you know, one of the potential delays in product development is what level of concern, or what willingness patients have to tolerate risk, and whether the regulatories and the regulator's perspective on that is different from the patient's. And I think there is a view that the patients are probably—are—maybe, in many cases, willing to tolerate more risk, particularly in serious and life-threatening illnesses.

So it seems to me, you know, from my observations, that there is a lot of recognition that the patient perspective is important, and the difficulty is, you know, capturing it both, you know, individually and aggregately, and how do you make a regulatory process that might even have to be adjustable based on individual patient preferences for balancing benefits and risks. So their interest is there, but I think it is complicated.

Mrs. ELLMERS. It is complicated, and certainly liability plays into all of this as well.

It looks to me, you really want to comment on this.

Mr. SASINOWSKI. I do. I do, because——

Mrs. ELLMERS. I would like——

Mr. SASINOWSKI. Because Congress deserves a great deal of credit, and as the lawyer understands the drug law, a 1906 drug law was created, it never mentioned—no law until FDASIA ever mentioned patient. It was assumed that laws could be created in order to enable a regulator to look at what the medical industry and the drug industry produced in some sort of paternalistic way for patients.

Mrs. ELLMERS. Um-hum.

Mr. SASINOWSKI. Now I am speaking on behalf of NORD, who represents 30 million Americans with rare diseases. And so we are so pleased that this Congress in FDASIA introduced the concept for the first time that the patient voice is meaningful, has a role in drug development, and that is why you had the patient focus drug development, the structured benefit risk ratio. The FDA said we can now empanel—the FDASIA law said empanel patients in part of the FDA internal review team as special Government employees. Tiffany House with Pompe Disease did that for a drug for Pompe, and the FDA reviewers, later when I talked to them, I said what did you learn from having a patient for the first time as part of your internal review team? They said we learned that for a patient with a relentlessly progressive deteriorating disease, that for that patient to be stable was a huge win.

So the role of the patient is now emergent, and it is due to this Congress. So I just couldn't avoid taking the time to say thank you.

Mrs. ELLMERS. Thank you to the panel. And thank you, Mr. Chairman, I know we went over our time, but I really could not avoid hearing those thanks and appreciative words. So much of what we typically do not hear. So thank you.

Mr. PITTS. The Chair thanks the gentlelady. And thank you for your remarks.

The Chair recognizes Mrs. McMorris Rodgers 5 minutes for questions.

Mrs. MCMORRIS RODGERS. Thank you, Mr. Chairman.

Would any of you, and maybe specifically Ms. Radcliffe or Dr. Neil, speak to the bureaucratic or regulatory burdens faced in starting or conducting clinical trials? And when was the last time that we, as a Nation, or Congress addressed the regulatory framework which governs how clinical trials are conducted, and do you think it is time for an update, given new technologies we can now bring to bear?

Mr. NEIL. Yes, I do think that this is an important issue, as I said previously, which is impacting the speed of development and its cost, especially, and also its effectiveness. So I do think this is worth a re-examination. I think there are a lot of things that we could potentially do at the statutory level. And here, I am thinking about standardized contracts for investigators, institutional review boards, safety monitoring boards which could be set up at the national or regional level, rather than the inefficiencies of having to establish these at every institution, and not having people who are necessarily as professionally qualified and experienced in monitoring these types of studies as they could be, as examples. And I think that working through public-private partnerships, or possibly authorizing additional money through the NIH to allow these trial networks to be established would also be a great help.

Ms. RADCLIFFE. Yes, I recommend Dr. Neil's testimony as a fairly comprehensive list of some of the things that could be done to expedite clinical trials. For BIO specifically, we have launched an initiative to look at 4 things. One is central IRB's, that is to streamline the review of protocols when they extend over multiple academic centers. The qualification process for drug development tools, such as biomarkers, and we have talked a little bit about that earlier in this hearing. Clinical trial networks. One of the great advantages of establishing clinical trial networks is to speed up the patient recruitment process which, today, is very much longer than it has been in the past. And so we could really make great inroads to addressing that issue. And finally, adopting a risk-based approach to clinical trial monitoring using centralized monitoring mechanisms. So those are 4 areas where we really want to make some progress at BIO over the coming years.

Mrs. MCMORRIS RODGERS. Thank you. Thank you.

Like many, I have been following the story of an innovative company, 23andMe, which developed a DNA testing kit that allows individuals to see which diseases or conditions they may have a predisposition to. And it seems to me that alerting individuals that they are more likely to have a certain disease or condition is a good thing, and it could be something that aids the development of new and innovative cures. For example, the genetic make-up of an individual who carries the gene for Huntington's Disease but does not suffer from the symptoms could be analyzed to determine what is his specific biology that stunts the development of that awful disease.

So the question, are products like this making a major step towards personalized medicine and tailor-made cures, and what does it mean for millions of people to be able to have crowd source—to be able to crowd source their genetic information? Anyone that may want to answer.

Ms. RADCLIFFE. All right, I will answer. We are—in the biotechnology industry, we are extremely excited about the potential for the use of genetic information in the design of clinical trials, and the expediting of those clinical trials, and also in healthcare delivery to help physicians and patients understand the best course of action. I think it is also important to understand though that information needs to be delivered in a way that enables the best decision-making by patients. A very specific example is that a patient might receive information about a risk of a certain type of cancer, and take action on that in a way that really would be detrimental to that person's health. And so as all of this wonderful information comes out, and as it is made available more broadly, we also have to put a great deal of thought toward the context for delivering that health information in a way that is helpful and not harmful.

Mrs. MCMORRIS RODGERS. Then would you speak to the role that FDA is playing in the process, and has FDA promoted the development of these kinds of diagnostic test? Is the FDA approval process adequately equipped to consider these types of products?

Ms. RADCLIFFE. This is an area where BIO has worked for a long time with FDA. The products that are coming out are so novel and so different from those that have been reviewed by FDA in the past, that they really require a different kind of scrutiny and different expertise. FDA has done a lot to improve that regulatory process, and to ensure that it has the expertise internally to manage these new technologies. I think that in the future, there will be a need for FDA to continue evolving to make sure that it is keeping up with the pace of scientific advances.

Mrs. MCMORRIS RODGERS. Thank you. And I too want to thank the panel and for everyone for participating. I am very excited about this 21st Century Cures Initiative, like everyone.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognize the gentlelady from Tennessee, Mrs. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman. And I want to thank each of you for taking the time to be here, and I apologize that we have been jumping up and down from the first floor where we have Chairman Wheeler with the FCC with a hearing going on, and I know for some of your groups, having access to broadband for some of the new medical apps, for telemedicine concepts, things of that nature, is very important. It is important to us also. So we have been in and out of that hearing.

I have been pleased to catch some of the comments about clinical trials and looking at those meaningful outcomes of bringing patients into that process, and we were discussing this in our office this morning. Dr. Summer, who is—does our health policy in the office, and I were talking about how important that is to have that impact. And my experience, you know, you have health professionals like Mrs. Ellmers and Dr. Cassidy and Dr. Burgess that are on this panel, but I come from the other side as a community volunteer who was chairman of the board for the Lung Association, on the Heart Board, the Arthritis Board, Children's Hospital, those components there in Nashville. And realizing as we put the emphasis on different participation for managing disease like asthma and

the outreach we did with the Lung Association, how important it was to hear from those patents and those patients of how different protocols and therapies affected them, and what the outcome was, and the importance of finding something that worked.

And, Dr. Radcliffe, I think it is the reason it was so—when I went to the State Senate in Tennessee, I took the initiative of working with a colleague, and we pulled together a biotechnology task force to begin to look for some of those personalizations that can come about in the medical field for treating these—the diseases that impact us. So I have enjoyed hearing your comments today, and appreciate that you all would take your time.

Just more one question I want to add to the mix here. And, Dr. Allen, I am going to come to you on this. We have had a little bit of discussion this morning as we have looked at Section 903 in FDASIA, and being able to pull those external experts into the process, and, of course, the conflict of interest, things of that nature, always has been such a problem, but I think that for those of you who are medical professionals, and for those like me who want to find answers and find a way to cure some of these diseases, having that participation is vitally important. And so I would just ask you, how is the FDA doing as it comes to the involvement and making it possible for some of these experts to openly participate, be full participants, in this process, which is what we are going to have to have if we get to some of these answers?

Mr. ALLEN. Right, so I think some of the panelists have already commented on bringing the FDA's efforts, and bringing patient expertise to the process and how important that is, in addition to Section 903 that you mentioned, bringing subject matter experts into the review process. And I think that was a very important component of FDASIA to expand on activities that the FDA was already doing, and might be able to even enhance through 903, and making sure that there were diverse experts in really subsets of specialties like rare diseases, or in different genetic diseases, to make sure that they had access to them.

You know, again, this goes back to resource-constrained agency. They simply will never have all of these experts, and particularly, as medical therapy becomes more and more diverse and specialized. So I think the—Section 903 provides one way to allow experts to be more involved in review, and I think we all can agree that we would like to see the FDA continue to implement that as rapidly as possible. I think even there is opportunity beyond just Section 903, which is really focused on involving expertise in the review process, but even things with not just the specific review, for things like developing best practices and guidance documents, there is a real opportunity to also call on those experts and those patients to make sure that they are able to contribute to the many diverse and important things that the FDA is charged with carrying out. And they continue to have more and more responsibility, and, unfortunately, not the resources to go along with that, so this is one way to help open those doors.

Mrs. BLACKBURN. We will continue to hold them accountable. Thank you, sir.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognize the gentleman from New York, Mr. Engel, 5 minutes for questions.

Mr. ENGEL. Thank you, Chairman Pitts, and thank you, Ranking Member Pallone, for holding today's hearing. I am pleased that this committee is focusing its efforts on the 21st Century Cures Initiative, and the President's Council of Advisors on Science and Technology, PCAST, Report, on Drug Innovation.

I believe that some of the best work that this Congress did during the 112th Congress was in working together to pass FDASIA. I have always been proud to serve on this committee because of the tremendous impact laws that originate within this committee can have on medical research and disease treatments.

The 21st Century Cures Initiative proves that this committee's commitment to getting new treatments into the hands of patients as quickly and safely as possible remains strong.

So let me ask you, Dr. Neil, in your written testimony, you suggested that Congress target its efforts in several different ways; one of which, and I quote you, was "to ensure that the FDA has adequate resources to do their job." I think it is critical the FDA—that the FDA does have adequate funding and staff resources in place in order to meet the demands of increasingly complicated and advanced medical therapies. I know there was significant frustration last year when sequestration caused $85 million in pharmaceutical and medical device company paid user fees to be unavailable to the FDA. Fortunately, the fiscal year 2014 Omnibus Appropriations Act restored the ability and the availability of these funds to the FDA. However, beyond funding, Dr. Neil, you mentioned that, and again, I am quoting you, "new trial designs and clinical endpoints will require collaborative efforts with academics and patient advocacy groups."

So could you elaborate on how academics and patient advocacy groups can better assist the FDA with the resources they need to meet the demands of 21st century medical treatments?

Mr. NEIL. Yes, thank you very much, Mr. Engel. I believe that FDA should be given more resources so that they can engage consultants, convene meetings with outside experts and also with patient advocacy groups to a greater extent. And I also think part of their—this new resources allocation that they might get beyond their base budget funding could allow them to hire more staff that could engage with small companies along the way to be able to guide them through the process more efficiently. I think they don't have enough money right now to be able to support the sort of scientific work that they need to do, in other words, there could be a lot more scholarship and original research in the areas of regulatory science that impinges on all of this inside the FDA, both an intramural and extramural program, and also the ability, just simple things like being able to travel to scientific meetings, I know that that is constrained right now too. And all of these things would help them to be able to create a more scientific culture internally, to be apprised of the latest advances in science, and to be able to incorporate that as they need to in their review process.

Mr. ENGEL. Well, thank you.

I mentioned to Dr. Woodcock during our last FDASIA hearing in November 2013, but I am particularly interested in the develop-

ment and approval of drugs for rare diseases. I am a co-author of the Paul D. Wellstone muscular dystrophy community assistance, research and education amendments of 2008 and 2013. I did it in conjunction with our colleague, Representative Burgess, and one of the aspects of FDASIA I am most interested in is the improvements made to the various expedited approval pathways, and the establishment of the breakthrough therapy pathway. To me, diseases like muscular dystrophy are why the expedited approval pathways are so important. One type of muscular dystrophy, Duchenne Muscular Dystrophy, is the most commonly lethal genetic disorder of children worldwide, affecting 1 in every 3,500 live male births. There is no cure, it is always fatal, and often at a young age, so the best hope for those with Duchenne is to treat the symptoms and delay its progression. However, in recent years, the muscular dystrophy research pipeline has held much promises, potentially life-saving therapies appear on the horizon, some of which are a result of Congress' efforts to improve research into this spectrum of muscle-weakening diseases through the MD Care Act, which was first passed and signed into law in 2001.

So it would appear to me that establishing quality intermediate endpoints that can add value to future trials is vital for experimental medications to be considered under the various expedited approval pathways.

So my question is recognizing the significant challenges that exist in developing therapies within the rare disease space, how can the FDA, NIH, drug companies and patient advocacy organizations better work together to ensure proper parameters for success and failure, being established through the critical trial process? Anybody want to comment on that?

Mr. SASINOWSKI. Well, Congressman Engel, I couldn't applaud you more for your work in the area, and with the MD Care Act and others, for reaching out to these communities of patients with rare diseases. So thank you for your work in that area.

I think that my testimony—my written testimony, I tried to describe what I thought would be four proposals that would advance the interests of those with rare diseases. I think number one is, you know, to again have FDA use accelerated approval more often. As I noted in my written testimony and my oral statement earlier, that when we looked at all of the use of accelerated approvals since FDA started it for the AIDS crisis in the mid-'80s through June 2013, there were only 19 drug therapies that the FDA had approved with that pathway that were not for cancer and not for AIDS. So it has to be used for these rare diseases, because in these rare diseases, we are looking, just as you said, Congressman, we are looking for something—an endpoint in a trial design that is something short of the ultimate clinical benefit. We don't want to have a clinical trial that is going to follow DMD boys all the time until they lose ambulation. And that is the ultimate clinical benefit, and we don't have the luxury to design clinical trials because we don't have enough boys and we don't have enough time. So we need to establish these other endpoints, and I think accelerated approval would help us do it, and I think this committee has done a great deal in FDASIA, and I think that there is more though that can be done.

Mr. ENGEL. Thank you.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentleman from Louisiana, Dr. Cassidy, 5 minutes for questions.

Mr. CASSIDY. I am sorry, I came in late, so if someone has already answered this. Several of you, and I think the PCAST recommendations speak of increased NIH funding, and decry the fact that since '03, there has been some decline. And reality is we have constrained Federal resources.

So with that context, there was an IOM report or GAO, I can't recall, from about 20 years ago suggesting that the NIH should reprioritize its funding priorities, and better reflect current needs. Frankly, I think when I looked at it a couple of years ago, they had not done so.

Now, do you have any thoughts on whether or not the NIH is appropriately allocating its resources to our current funding needs? I look at Alzheimer's, I think it may be getting $600 million, but the cost of future Alzheimer's is huge.

Ms. Radcliffe, do you have any thoughts, just to call upon you?

Ms. RADCLIFFE. First, thank you for highlighting the importance of continuing to fund the NIH. As you noted, the real——

Mr. CASSIDY. Yes, I got that, but——

Ms. RADCLIFFE. Yes.

Mr. CASSIDY [continuing]. Frankly, we don't have enough money. So my real question is, my pointed question is, does the NIH need to reallocate some of its assets, because, again, the IOM suggested this 20 years ago, I am not sure it has been done since.

Ms. RADCLIFFE. Yes, so we have been extremely supportive of a new center at NIH called the National Center for Advancing Translational Sciences, NCATS, and we are extremely interested in supporting the work of that center——

Mr. CASSIDY. I——

Ms. RADCLIFFE [continuing]. Because it will more directly lead to——

Mr. CASSIDY. I hear what you are saying. I have limited time so that is not really what I am asking.

Dr. Neil, any comments upon what I just suggested?

Mr. NEIL. I think they are doing a very good job, actually, in prioritizing at the moment. One wishes that one could predict where important discoveries were going to come from, but——

Mr. CASSIDY. Now, let me ask you, it isn't so much to predict important discoveries, it is the fact that we have this incredible challenge of neurodegenerative diseases. I mean that is just out there.

Mr. NEIL. Right.

Mr. CASSIDY. And if you look at what we are funding that with relative to other diseases and their future cost, which is easily predicted, it seems perhaps, again, a different priority than others would select if you could just start over. So any specific—again, people may be hesitant to criticize NIH, but if we are asking for more funding, we have to also know they are using their funding wisely.

Mr. NEIL. Yes. I just wish that one could, again, really think about how to prioritize and manage it, but we don't know where

a discovery in a completely different area that affects mitochondria or who knows what may be the breakthrough that we need in neurodegenerative diseases.

Mr. CASSIDY. You are suggesting that we need to have no direction whatsoever, I think I am—I think is what I am hearing from you, but rather rely upon kind of basic research to produce.

Mr. NEIL. Well, I don't think it is just that, but I think that the most promising basic research needs to be funded if we are going to continue to advance.

Mr. CASSIDY. Mr. Sasinowski, any thoughts?

Mr. SASINOWSKI. Yes, it—with your particular concern about neurological, neurodegenerative diseases, yes, a large swath of the rare diseases in this country fit into that category. And as, you know, Dr. Neil just mentioned, you know, the underpinnings, the pathophysiology of many of those go back to mitochondrial energy production. So if we could have reallocation of NIH funds that would redirect it to some of these areas that have the promise of being able to address a lot of diseases, that might be a worthwhile endeavor.

Mr. CASSIDY. It seems like we should have some metric; what is the future cost, what is the current morbidity, and have it reflect that.

Dr. Tunis, you know, I used to do medical research. My nurse who I worked with, who basically told me what to do when I showed up, said, man, the paperwork has increased dramatically over the years. Now, one of the recommendations, I think number seven, suggests that maybe FDA could be more efficient in terms of how it does it process. I am asking you just to ask, it could be anyone, how would you grade what FDA has done in terms of, is the monitoring process thoroughly useful, or is some of it kind of, oh, my gosh, why in the heck are we doing this? It is just driving up cost. Any kind of a—any kind of grade you would give the FDA for their current efforts?

Mr. TUNIS. Well, I think—I would hate to grade FDA, but I think FDA actually recognizes that there are a lot of this excessive activities and cost embedded in clinical trials, and one of the things, again, Garry and others know a lot about is they do have this partnership with Duke called the Clinical Trials Transformation Initiative which is systematically trying to identify where there are, you know, excessive regulatory burdens, things that contribute to the inefficiency of clinical research, and, you know, doing—you know, exploring how those things could be minimized. So I would give the FDA an A grade in terms of identifying that there are opportunities to improve, and having at least that forum to, you know, to look for solutions. And I don't know if, Garry, you wanted to add anything to that.

Mr. NEIL. Well, the—monitoring is a particular issue that we took on with TranCelerate, and FDA provided input into that, and we know that we are overdoing this in ways that are not really adding value, maybe subtracting value and driving cost, so moving to a more risk-based monitoring approach, again, with FDA——

Mr. CASSIDY. Any sense of how much cost that adds? Five percent, 10 percent, marginal cost of——

Mr. NEIL. It——

Mr. CASSIDY [continuing]. Monitoring which may be inefficient?

Mr. NEIL. It depends on the trial, obviously, but—and I can't give you a precise estimate, but it is very substantial.

Mr. CASSIDY. Very substantial.

Mr. NEIL. Very substantial.

Mr. CASSIDY. OK. That was kind of my impression from being frontline way back when.

Thank you very much. I yield back.

Mr. PITTS. The Chair thanks the gentleman.

That concludes the first round of questioning. We are going to go to one follow-up per side now.

I will recognize Dr. Burgess 5 minutes for his follow-up.

Mr. BURGESS. Thank you, Mr. Chairman, and again, I want to thank the panel for being here. It has been a long morning but a very informative morning. I would be remiss if I did not acknowledge, I guess, my co-sponsor, Eliot Engel, has left, but the MD Care Act, Mr. Chairman, that is a good Bill and one that I hope we can have a legislative hearing and a markup on before we get too deep in the political season, because it is one that needs to occur, and, in fact, the last reauthorization—we haven't addressed the problem that occurs that we are doing such a good job, some of these patients are now living until early adulthood when they didn't before, and the current Act does not address young adults with the illness, and we need to do that. So I hope we can have that legislative hearing.

I also, Mr. Sasinowski, I don't want to correct you, but it was actually the last Congress that passed FDASIA, but it was this committee that did the work, and I just wanted to acknowledge the work of Brian Bilbray, who is no longer with us, and really it was his—I mean he was a bulldog on the surrogate endpoints when FDA was in testifying before this committee. And without Brian Bilbray's contribution, I don't think FDASIA would have been as effective, and, of course, the—I certainly—I appreciate the hearing this morning about the conflicts, the trying to improve the status of the conflicts language so that we could improve the advisory panels that we empanel to advise the FDA on approvals.

Look, one of the things that the President's council did come up with and talk about was the woeful state of the information technology at the Food and Drug Administration. You hear the urban legends about the warehouses of new drug applications that are in boxes on paper applications in the basement somewhere. I don't know whether it is true or not because I have never seen it, but can anyone speak to—I guess there has been the hiring of a new chief information officer. Does anybody see any daylight on the horizon there? Apparently not.

Let me just tell you what is so frustrating. This committee, for the last—I have been on the committee for 10 years, and we have had this discussion over and over and over again. As a practicing physician, I have received the slings and arrows because doctors' offices are not coming into the information age rapidly enough, and here we have the FDA which is just stumbling all over itself. I mean surely there is something we can do about that to digitize the data. I mean if this were a class action lawsuit, the large litigation firms around the country would get together, digitize the data and

analyze it in a weekend, and we can't do it as a Federal agency. I don't know, surely somebody has some thoughts on how to improve this system. Again, let the—for the clerk's benefit, no one volunteered an answer. I just—I acknowledge this is something that needs to be fixed. I appreciate Dr. Cassidy's comments about the funding constraints, but if we don't fix this, we are not getting out of this problem.

I do want to ask Mr. Sasinowski, probably the one thing I have heard this morning that I am going to take with me out of this hearing is that perhaps the default position that the FDA ought to be the accelerated pathway. And the FDA historically has been risk averse, but you are talking about a new world order where the FDA now defaults to the accelerated pathway. So can you speak to accelerated approval as the default in the future?

Mr. SASINOWSKI. Yes, Dr. Burgess, that the—I don't see it as a default. I don't see most of the therapies coming through the FDA's gauntlet, being approved under accelerated approval because it only fits for those which are serious diseases where there is an unmet medical need, but what I am saying is that those twin criteria could apply to many diseases, especially the rare diseases, the 7,000 rare diseases that affect Americans, and so for those, you know, that should be part of the discussion at the beginning, at the pre-IND meeting, when we are first coming into the FDA, that should be part of that engagement, because you have heard several other witnesses, and it was also in FDASIA and PCAST, that said if you are going to go forward with accelerated approval, you have to start that discussion early because you have to be able to identify the surrogate endpoints, and the intermediary clinical endpoints so that you can run the studies in the proper way. And so that discussion is not going on. So what I was suggesting, Dr. Burgess, is that every time that a new therapy is proposed to the Agency, one of the first questions always be, as part of their checkbox, is this a candidate for accelerated—would this fit, is this a serious disease for which there is an unmet medical need, and then the system can integrate that. And it is currently just not being considered.

Mr. BURGESS. Not only is it not being considered, but I will just tell you, not a month goes by that someone is not in my office with a tale of woe——

VOICE. Yes.

Mr. BURGESS [continuing]. About getting their drug or device approved, and I for one, in this committee, I am just tired of hitting my head against that wall, and it is time for us to break through or break out of that modality and move into the 21st century.

Thank you, Mr. Chairman, for holding the hearing. I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

That concludes the questions at this point.

The Members will have follow-up questions. We ask that you please respond promptly.

This has been a very informative hearing. We appreciate you sharing your expertise with us and the practical recommendations.

I remind Members that they will have 10 business days to submit questions for the record. Members should submit their questions by the close of business on Tuesday, June 3.

Without objection, the subcommittee is adjourned.

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

[Material submitted for inclusion in the record follows:]

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

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June 10, 2014

Dr. Garry A. Neil
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Dear Dr. Neil:

Thank you for appearing before the Subcommittee on Health on Tuesday, May 20, 2014, to testify at the hearing entitled "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Tuesday, June 24, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Garry A. Neil, MD
June 24, 2014

The Honorable Gus Bilirakis

1. One mechanism drug companies have to improve certainty about the Agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract?

   Answer. PDUFA specifies three categories of eligibility for special protocol assessment: 1) animal carcinogenicity protocols, 2) final product stability protocols, 3) clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim. The protocol is most often used by small companies who are seeking more certainty and who may not have the resources or time to withstand the need for additional studies. An SPA is generally binding upon the FDA unless a substantial scientific issue essential to determining safety or efficacy is identified after the testing begins. It therefore cannot and should not be viewed as a "contract" with FDA guaranteeing approval if the endpoints in trials are met. I believe in most cases the agency has honored the agreement, but I have not been able to obtain data to date. Furthermore, I am aware that there have been several high visibility cases where FDA has required additional studies despite an SPA agreement. I have not used the SPA process personally - instead preferring to work with FDA throughout the development process and to develop a program based on their input at end of phase II. This has generally succeeded when the data support the intended use. I do think that clarity of message and communication is critical and can be improved. Some Divisions of FDA seem to provide better clarity than others. I believe that FDA should strive for consistency across its Divisions to the extent possible and be resourced to provide more meeting time with sponsors for clarification. Perhaps a formal survey of sponsor satisfaction on the process after an action is taken would be useful for the Agency and Congress.

2. For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate end points That is reasonably likely to predict a clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can FDA work with stakeholders to determine endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?

   Answer: This is a very significant issue because lacking acceptable endpoints repels investment in many serious diseases. FDA has been (understandably) reluctant to accept non-validated surrogate endpoints presented by individual sponsors for use with specific therapies. This is usually because of a lack of data that would support generalizability as well to accurately predict a real clinical benefit. Individual sponsors have a very difficult time overcoming this – as well as issues of time and cost. However, there is an opportunity for public private partnerships that include NIH and FDA as well as patient advocates and industry to address this. The Biomarker Consortium[1] (managed by the Foundation for the NIH) is one such partnership that I have been involved with since its inception in 2006. It is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health that endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics. Founding members include the NIH, FDA, CMS, BIO, PhRMA and several pharmaceutical companies. A number of important studies have been conducted and are underway.

[1] https://www.biomarkersconsortium.org

Additional efforts need to be undertaken. I believe that in many cases it would be possible to develop provisional surrogate markers based on consensus of leading academics, patient advocacy groups and the FDA. Such markers could be used to develop new therapies now, with additional evidence developed with longer-term follow-up. Some of these markers will thus be validated whereas others may be shown to be less reliable of definitive outcomes, resulting in label changes as appropriate, or in some cases even product withdrawal. Such provisional markers could be proposed by consensus conferences under a public private convening organization such as the Regan-Udall Foundation and could be further assessed by FDA advisory committees if needed. I would urge Congress to commission further study of this topic and to assist in any way possible to expedite implementation of strategies to accelerate surrogate and clinical endpoint development.

3. What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?

Answer: Real world data, that is data that are collected outside clinical trials, are abundant and contain a wealth of information. Unfortunately, these data remain difficult to efficiently access and analyze. A major problem with most observational data is an inherent inability to correct for unmeasured confounders and biases. Nevertheless, such data are very useful to monitor costs and quality, to assess use patterns of physicians and to generate hypotheses for further testing. Widespread use of electronic health records (EHR) will substantially increase the availability of richer clinical data sets. However, EHRs are designed to meet clinical practice needs. Successful use of EHR for clinical research requires that a number challenges be overcome. These include the need to integrate information technology (IT) systems, reconciliation of different terminologies and managing numerous regulatory and institutional requirements that do not support EHR use for clinical research[2]. Mandating data and regulatory standards for EHR including the ability to use de-identified data in limited ways as part of the consent for treatment at every clinic and facility would help to facilitate such studies.

Randomized trials are expensive and have been criticized as lacking applicability to clinical practice[3]. However, at present confounding and bias can only be effectively managed by randomization. New randomized trial designs have recently emerged that address these issues. Pragmatic trials are conducted in real-life settings encompassing the full spectrum of the population to which an intervention will be applied[4]. As long as patients are selected for a given therapy randomly to avoid selection bias by the physician data derived from such studies may have value for patients, practitioners, policy makers and the biopharmaceutical and medical device industries alike. As I mentioned in my previous written testimony one of the most interesting experiments currently underway is the NIH Collaboratory project[5].

On their website, Collaboratory describe themselves as follows: "Supported by the Common Fund at the National Institutes of Health, the Health Care Systems Research Collaboratory is intended to improve the way clinical trials are conducted by creating a new infrastructure for collaborative

research. The ultimate goal is to ensure that healthcare providers and patients can make decisions

[2] http://www.clinicalresearchforum.org/EHR4-4-14_white_paper_draft.pdf
[3] Why are so few randomized trials useful, and what can we do about it? Zwarenstein M, Oxman A, Pragmatic Trials in Health Care Systems (PRACTIHC). *J Clin Epidemiol.* 2006 Nov; 59(11):1125-6.
[4] A pragmatic view on pragmatic trials. Patsopolous, N. *Dialogues Clin Neurosci.* Jun 2011; 13(2): 217–224.
[5] http://www.nihcollaboratory.org

based on the best available clinical evidence. The NIH HCS Research Collaboratory also supports the design and rapid execution of several high-impact Pragmatic Clinical Trial Demonstration Projects that will address questions of major public health importance that engage health care delivery systems in research partnership." The group is led by outstanding clinical investigators and merits close observation. More such efforts should be encouraged by Congress.

However, in addition we should also strengthen and improve our conventional randomized control trial infrastructure by encouraging more patients to enroll, facilitating creation of standing clinical trials working groups and examining ways to reduce the cost of monitoring based on need and risk.

4. Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leveraged for supplemental applications?

   Answer: I respectfully disagree with that assertion by PCAST. Formal approval is more important than ever for compliance purposes, especially given recent aggressive enforcement. Additional research investment to expand the indications or dosing regimens for an approved product is usually very lucrative for a manufacturer. Such studies are usually lower risk than pursuing new molecules, and also expand the safety database. In my experience, it has not proven difficult to find patients for new studies of drugs that offer real benefit, address areas or real need and answer questions of real importance to the ecosystem. That said, the efficiencies of trial execution in general should be greatly improved to lower costs and shorten timelines for the benefit of the entire ecosystem.

   When patient populations are small and diseases are very serious and/or life threatening (such as rare and orphan diseases, certain cancers), most patients will understandably not want to be randomized to placebo or less effective therapies. In these cases, trial designs that compare multidrug regimens, higher or lower doses, new dosing regimens are feasible in my experience and allow valuable new information to be gained, new populations to be studied and the safety database to be expanded.

   Sponsors have also been criticized of "dragging their feet" on performing post approval commitment studies. In my experience, this is not the case, although FDA has sometimes requested studies that are difficult to perform due to lack of patients. Sponsors sometimes agree to perform such studies in order to gain approval without carefully analyzing the feasibility of the trial. Once again building a more robust clinical trials infrastructure including better means of identifying patients and the ability to perform "pragmatic trials"[6] should help. However, FDA now has broad enforcement power in this regard and compliance should not be an issue.

   I believe that real world (observational data) are very valuable and a number of policy issues to facilitate use of such data such as ensuring that patients consent to the use of their de-identified data in limited clinical research without the need for individual consent and IRB review. However, one can easily be misled by such observational data owing to the potential for selection bias by physicians, e.g., a new drug may appear to be associated with a higher incidence of side effects

[6] A pragmatic view on pragmatic trials. Patsopolous, N. Dialogues Clin Neurosci. Jun 2011; 13(2): 217–224.

than an older drug when the opposite is true because 1) the older drug may be less scrutinized, 2) the physician may select the new drug for her sicker patients believing it to be better with different outcomes. For these reasons we should continue to invest in pragmatic trials that allow randomization such as those currently being piloted in the Collaboratory[4].

5. As a Member of Congress, we hear tales about how companies meet with FDA on drug approval and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science?

Answer: As I noted in my answer to Rep. Schakowsky, I have interacted with FDA for more than 20 years. The large majority of FDA scientists are among the most dedicated civil servants one could ever encounter. Among them are former academics and industry scientists who moved to FDA to help advance innovation and to improve the public health. Some are among the world's best clinical scientists – even though they may not always be recognized as such. However, like every large organization, there are underperformers, although they are in the minority. It sometimes seems that senior FDA leadership do not currently have the tools needed to manage performance optimally. Thus consistency can suffer.

PDUFA has certainly improved the productivity of the agency and provided more rigorous timelines for review. However this has come at a price. FDA workload has outpaced their budget and staff. The intramural research program of FDA has been greatly reduced. FDA scientists have serious travel restrictions that do not allow them to attend scientific conferences as frequently as they should and to have meetings with leading academics. Thus the culture of the FDA has become increasingly "bureaucratized" and less scientific. One can contrast this culture with that of the NIH. Given the complexity of the new products in the pipeline including stem cell and gene therapy, smart devices and so on this does not bode for our competitive position in the world.

A number of the most senior and best scientists have or will soon retire. They will be difficult to replace. An increase in the budget for intramural science would attract higher quality scientists and raise their visibility in the academic community. The emphasis should be placed on clinical trials, regulatory science, toxicology, and other scientific disciplines directly related to the FDA mission. Increased budget for attendance at scientific conferences and training would also help. Top scientists should be recruited. Excellent performers should be rewarded and poor performance should be managed. Information management technology needs to be upgraded. Processes need to be improved so that busy work is reduced in favor of value added activities. We need to maintain a world class, science driven FDA. In my view, such reforms would greatly improve the culture, productivity and morale at FDA.

Beyond this, it is critical that FDA and sponsors communicate regularly throughout the development process so there are no "surprises" at the end. Additional bandwidth for meetings can help – especially for small companies. I believe FDA communication can and must be more specific to sponsors. It is not helpful to have to "read between the lines" to know that a program is not on track. Hiring additional FDA staff with small company experience to provide guidance would be helpful. Small companies are very fragile and significant change in timelines or additional unanticipated requirements late in the development cycle can destroy them – and worse deprive desperate patients of life saving alternatives.

The Honorable Jan Schakowsky

1. A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new hepatitis C drug treatment costs about $100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation?

   Answer: Thank you so much for this question. Pricing and affordability are certainly complex issues and I am not an expert in that area, but I will give my view. One of the greatest medical achievements of this century has been the curing of hepatitis C[7]. As a physician and scientist I must agree that innovation, even of this incredible magnitude and significance, that cannot be accessed is Pyrrhic victory. We must, therefore, work diligently to lower the cost of R&D, shorten the timelines and reduce uncertainty and failure. How can we do this? As I testified, we must invest in building an efficient infrastructure for clinical trials. Clinical trials working groups that are trained and ready to conduct studies on new products at every phase are needed. We should find ways to encourage and invest in creation of such networks. Industry itself is undertaking efforts to address issues of clinical trial cost and efficiency. Transcelerate Biomedical Inc.[8][9], a non-profit industry collaboration I helped found in 2012 is providing leadership in this area. The early results are very encouraging with more than 41,000 clinical investigators having been trained and a number of other promising initiatives underway - but much more needs to be done. More investment in surrogate markers and clinical endpoints is needed. The Biomarker Consortium[10] (managed by the Foundation for the NIH) is one such partnership that I have been involved with since its inception in 2006. It is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health that endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics. Founding members include the NIH, FDA, CMS, BIO, PhRMA and several pharmaceutical companies. A number of important studies have been conducted and are underway. We also need to continue to invest in FDA and public-private partnerships to support regulatory science including the Reagan-Udall Foundation[6]. Improving the capacity, training and culture of the FDA will also reduce uncertainty for both large and small companies to advance innovative products to accelerate and reduce the cost of innovation.

2. In your testimony, you stress the need to ensure that the FDA has the scientific workforce necessary to meet its regulatory mission that includes the ability to understand cutting edge technology and assess innovative products. You point out in your testimony that an important way to achieve this goal is to ensure adequate funding for FDA's intramural regulatory science programs. Would you discuss the importance of the regulatory science programs in enabling FDA to fulfill its mission of approving safe and effective drugs? Are there other ways that Congress can help ensure that FDA has the workforce to meet its needs?

   Answer: As I noted in my response to Rep. Bilirakis, I have interacted with FDA for more than 20 years. The large majority of FDA scientists are among the most dedicated civil servants one could

[7] Curing Chronic Hepatitis C — The Arc of a Medical Triumph. Raymond T. Chung, M.D., and Thomas F. Baumert, M.D. N Engl J Med 2014; 370:1576-1578
[8] Drug Makers Join Efforts in Research, Andrew Pollack, New York Times. Sep. 19, 2012
[9] http://www.transcelerateblopharmainc.com
[10] http://www.biomarkersconsortium.org

ever encounter. Among them are former academics and industry scientists who moved to FDA to help advance innovation and to improve the public health. Some are among the world's best clinical scientists – even though they may not always be recognized as such. A number of important contributions to the scientific literature are made by FDA scientists each year. These FDA scientists can make even more important contributions to original clinical and regulatory science if they are given the time and resources to pursue these activities. We must be cognizant that a number of the most senior and best scientists at FDA have or will soon retire. They will be difficult to replace.

PDUFA has certainly improved the productivity of the agency and provided more rigorous timelines for review. However this has come at a price in my view. FDA workload has outpaced their budget and staff. The intramural research program of FDA has been greatly reduced. FDA scientists have serious travel restrictions that do not allow them to attend scientific conferences as frequently as they should and to have meetings with leading academics. Thus the culture of the FDA has become increasingly "bureaucratized" and less scientific. One can contrast this culture with that of the NIH. Given the complexity of the new products in the pipeline including stem cell and gene therapy, smart devices and so on this does not bode for our competitive position in the world.

In my view, an increase in the budget for intramural science would attract higher quality scientists and raise their visibility in the academic community. The emphasis should be placed on clinical trials, regulatory science, toxicology, and other scientific disciplines directly related to the FDA mission. Increased budget for attendance at scientific conferences and training would also help. Top scientists should be recruited and retained. More interactions and cross appointments at NIH should be available. Academic rotations and even rotation of industry scientists to the FDA (with appropriate manage of conflict of interest) should be explored.

In addition to increasing resources, other reforms could also help. Excellent performers should be rewarded, with respect to both regulatory reviews but also scholarship and leadership. Poor performance should be managed. Nothing demoralizes an organization more than tolerance of under performance, increasing the burden on the productive staff. Information management technology needs to be upgraded. Processes need to be improved so that busy work is reduced in favor of value added activities. Peer review including more outside review of FDA science would be helpful as well. In my opinion, all of this would increase morale, productivity and greatly enhance the culture of the world's best regulatory agency – making it even better.

3. I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIH is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIH means to the pace of drug innovation? How has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?

   Thank you for your important testimony. Your testimony makes clear the harm caused by inadequately funding the NIH. I hope that we can work together to ensure that NIH has the resources it needs to ensure that we remain the world's leader in innovation and that we accelerate our ability to discover new treatments and cures that save lives and improve health.

Answer: The failure to at the very least maintain purchasing power at NIH puts the entire biomedical research enterprise at risk. NIH funding is critical to finding the next generation of cures AND in maintaining our competitiveness globally. In industry our success is largely based on the enormous body of scientific work produced by NIH funded research. There is an implicit partnership that has been extraordinarily complementary and effective. We simply cannot come close to replacing this amazing enterprise that has done so much for to advance the health of Americans and people around the world.

Training has always been an integral and critical component of the NIH mission. Fewer of the best and brightest minds are choosing an academic career because of the extreme difficulty they face in obtaining funding from NIH. Many established scientists are likewise leaving the bench in favor of other careers. I had the privilege of working on a Working Group commissioned by NIH Director, Dr. Francis Collins in 2011-2[11]. We found that 30% of biomedical PhD's pursue careers in the biotechnology and pharmaceutical industries. Thus one can expect a diminution in the pool of qualified scientists who will translate basic discoveries into new medicines. Some of these scientists can and will be replaced by foreign scientists and some research and development can and will also be moved abroad to take advantage of pools of talent, but in general this does not bode well for the health of the ecosystem or competitiveness of the US.

We are now on the threshold of the next generation of medicines – gene therapy, stem cell therapy and other interventions that could not have been dreamt of just a generation ago. We are also facing a crisis in health care that is largely the result of so many chronic and expensive illnesses. We are also facing many challenges to our global leadership in biomedical research and development that has contributed mightily to our prosperity and standing as a nation. We cannot and must not fail to continue to invest in NIH and FDA to ensure that we will find solutions to the diseases that are causing so much suffering in the US and abroad, maintain our competiveness and reduce the cost of health care for all Americans. I can think of no better use of our precious tax dollars and nothing that would ultimately create a higher return for our citizens.

[11] Biomedical Research Workforce Working Group, Draft Report National Institutes of Health, June 14, 2012 http://acd.od.nih.gov/bmw_report.pdf

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June 10, 2014

Ms. Sara Radcliffe
Executive Vice President, Health
Biotechnology Industry Organization
1201 Maryland Avenue, S.W., Suite 900
Washington, D.C. 20024

Dear Ms. Radcliffe:

Thank you for appearing before the Subcommittee on Health on Tuesday, May 20, 2014, to testify at the hearing entitled "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Tuesday, June 24, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Response from Sara Radcliffe, Executive Vice President for Health, Biotechnology Industry Organization

Attachment 1 Additional Questions for the Record

The Honorable Leonard Lance

1. ***Thank you for your testimony during the May 20 Health Subcommittee hearing on the President's Council of Advisors on Science and Technology Report on Drug Innovation. At the hearing, you testified about the extraordinary expense to bring a new drug, biologic or diagnostic to market and the critical importance of developing and ensuring policies that incentivize investment in the "next generation of biomedical discoveries, treatments and cures." I also agree with BIO's testimony that to ensure investments by venture capitalists, we need an "FDA regulatory framework that is predictable, consistent and well-resourced." The Special Protocol Assessment (SPA) process was created by Congress to create such a framework, and until recently, has promoted innovation and investment in the development of new medicines essential for patient well-being. Do you believe the integrity of the SPA process is essential to ensuring continued investment in biomedical research? If the Agency were to stray from statutory guidance in the SPA decision-making process, what impact would such actions have on the availability of private funding for research and development?***

The Special Protocol Assessment (SPA) process is intended to enhance predictability and consistency to drug development by ensuring that FDA and the Sponsors are in agreement on innovative clinical trials designs and study endpoints for the purpose of regulatory approval prior to initiation of the study. This confidence that FDA will accept the data culminating from these studies plays a role in helping companies attract long-term investment in multi-year clinical trials. However, the value of the SPA process is being publicly called into question.

It can often take several cycles of FDA review to achieve initial agreement on an SPA, which can lead to unnecessary delays in conducting trials. For example, a recent survey of BIO member companies found that 1 in 4 respondents had utilized the SPA process since 2010. However, 78% of SPAs required multiple 45-day review cycles to reach final agreement taking an average of three months to finalize the SPA.

Additionally, recent events have raised concerns about FDA's procedures for adhering to its commitments under an SPA, especially in instances where there may be inconsistent interpretations of the underlying science supporting the SPA. BIO would like to better understand FDA's interpretation of the standard and operating procedures by which FDA would rescind a SPA. Public skepticism about FDA's commitment to SPAs, including in the biotechnology and venture capital communities, could potentially erode the value of the SPA mechanism for drug and biologic sponsors.

The Honorable Gus Bilirakis

1. ***In the world of rare diseases or orphan drugs, there are almost 7,000 diseases affecting about 30 million Americans. Most of these diseases have no treatment. In the last FDA user fee agreement, Congress rewrote the***

statute on Accelerated Approval and directed FDA to expand the Accelerated Approval pathway beyond HIV / AIDS and oncology. The FDA has released guidance on the implementation of this expedited approval pathway. What is BIO's opinion of the guidance that was released? Do you feel confident that accelerated approval is being implemented the way Congress intended?

As part of the *FDA Safety and Innovation Act of 2012*, Congress explicitly encouraged FDA to more effectively utilize FDA's expedited approval pathways — including Breakthrough Therapy Designation and Accelerated Approval — to advance the development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions.

BIO was pleased to see FDA finalize the draft guidance on *Expedited Programs for Serious Conditions — Drugs and Biologics*. From a procedural perspective, this guidance will help Sponsors to better understand the unique qualifying criteria and features of each expedited program.

The final guidance includes new language to address several high-level issues raised in BIO's comments and those submitted by other stakeholders, such as:

- The importance of employing regulatory flexibility and expedited approval strategies for developing therapies to treat rare diseases (p.2, p. 15, p.21-22)
- The eligibility of vaccines and preventative therapies for expedited programs (p.3)
- Application of Accelerated Approval in acute disease settings (p.15-16.)
- Additional examples of surrogate and intermediate clinical endpoints (p. 18-19)
- Flexibility in manufacturing/CMC as an element of a post-marketing plan (p. 26)
- Discussion of companion diagnostics (p. 27)

We would like to continue to work with the Agency to ensure that these innovative approaches are fully embraced at the review division level across a wide spectrum of serious and life-threatening conditions.

To date, FDA has granted more than fifty requests for Breakthrough Therapy Designation in areas such as oncology (27%), hematology (19%), infectious disease (23%), and rare conditions.[1], [2] To date, FDA has reviewed and approved six Breakthrough designated products to treat cystic fibrosis, leukemia, lymphoma, hepatitis C, and lung cancer — many in record time after only 4-6 months.[3] However, it is unclear whether this program is being met with the same level of interest across all FDA centers and review divisions as is the case in the oncology and anti-infective review divisions.

FDASIA also expanded and modernized FDA's existing Accelerated Approval pathway, which can grant approval to a therapy for a serious or life-threatening disease on the basis of a surrogate or intermediate clinical endpoint that can be measured earlier in drug

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[1] Biotechnology Industry Organization (BIO), *Breakthrough Therapy Designation and Approvals*, updated June 2, 2014

[2]FDA, Dr. John Jenkins, Director, Office of New Drugs, CDER, *CDER New Drug Review: 2013 Update*, December 11, 2013, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM378227.pdf

[3] FDA, *Breakthrough Therapy Approvals*, *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373418.htm*

development. This may result in fewer, smaller, or shorter clinical trials for the intended patient population and can allow patient access to life-saving therapies years earlier than traditional approval.[4] FDASIA provides FDA with additional flexibility to accept novel study endpoints and employ the pathway in therapeutic areas beyond the traditional scope of HIV/AIDS and oncology. Since enactment of FDASIA, at least seven products to treat serious diseases have been approved under Accelerated Approval, including five in oncology, one in infectious disease, and one for the central nervous system. Given the limited number of approvals under the program and the multi-year drug development timelines, it is premature to assess whether the program is having its intended effect.

While FDA's procedural guidance is welcome, we have requested that the Agency clarify further the criteria for validating a novel endpoint for Accelerated Approval and the process for engaging FDA in that discussion earlier in drug development. For example, the guidance states that "determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment" and that "this guidance does not, however, address the specific clinical evidence needed to support a conclusion that a particular surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit or IMM because such evidence is case-specific and is not readily generalizable."

The 2012 PCAST report notes that "Drug developers have expressed frustration that it is difficult to get clear and timely answers concerning the acceptability of specific predictors for Accelerated Approval. Without such clarity, the risk of employing such predictors during the lengthy drug development process is often too great to justify significant investment." Indeed, a lack of process predictability and criteria for developing novel surrogate endpoints can potentially undermine the intent of the Accelerated Approval program.

2. ***One mechanism drug companies have to improve certainty about the Agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract?***

Please see our response on SPAs above.

3. ***For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate endpoints that are reasonably likely to predict a clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can FDA work with stakeholders to determine new endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?***

As discussed above, BIO believes that FDA's process around the utilization and acceptance of surrogate and intermediate clinical endpoints has been variable across review divisions. We look forward to working with the agency to establish clear lines of communication on discussing an endpoint to support Accelerated Approval early in development, and also evidentiary criteria for supporting that endpoint.

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[4] Johnson, Ning, Farrell, Justice, Keegan, Pazdur, *Accelerated Approval of Oncology Products: the Food and Drug Administration Experience*, Journal of the National Cancer Institute, February 7, 2011, http://jnci.oxfordjournals.org/content/103/8/636.short

FDA has been open to working with private-public partnerships and consortium to research new biomarkers and potentially new surrogate endpoints. However, to date progress in validating or qualifying these measures for regulatory purposes has been slow to produce new drug development tools that can improve the efficiency of drug development. For instance, since 2008 only three biomarkers have been successfully FDA-qualified, while scores of other potential biomarkers that are being developed by consortia are mired in the FDA consultation phase in order to clarify the context of use and determine the level of evidence need for qualification.

4. ***What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?***

Advancements in information technology and the adoption of electronic health records place biomedical sciences at the cusp of fully realizing a "learning healthcare system." Such a system can evaluate real-world data to assess the safety and efficacy of medical interventions, including drugs and biologics, to support the cycle of biomedical innovation from drug discovery and development to the point of healthcare decision-making. However, additional research and methodology development is needed to validate the use of real-world evidence to support claims of safety and efficacy.

As part of the Agency's Sentinel Network initiative, FDA has made considerable progress in developing the tools and methodologies for assessing post-market data to identify safety signals; we should continue to build upon that foundation to also consider efficacy endpoints. While the scientific methods in this area continue to evolve — and are evolving in particular through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program — we must embrace a future where FDA and industry can be aligned to better leverage real-world data to answer key research questions more efficiently than in large-scale randomized clinical trials.

Enabling the appropriate use of rapidly growing digital health information can help not only to inform regulatory approval and fulfilling post-approval commitments, but also in providing relevant information at the point of healthcare decision-making. Crucial to this effort will be broadening access to existing federal data resources — such as from Centers for Medicare and Medicaid Services (CMS)-administered federal healthcare programs, the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention — and standardizing the collection of these data across various sites of care to provide a comprehensive, continuous picture of an individual's health and the care he/she receives.

5. ***Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leveraged for supplemental applications?***

Continued technological advances in gathering and employing data have the potential to improve the timeliness of drug development. For example, while randomized, controlled clinical trials (RCTs) are considered to be the gold standard to assess safety and clinical efficacy, they often evaluate uniform populations remotely connected to the use of drugs in regular clinical practice or in settings reflecting real-world health care delivery. RCTs can

readily identify higher-frequency adverse events and assess clinical efficacy, but they must enroll thousands of patients to be powered sufficiently to detect rare adverse events or slowly progressing clinical manifestations. Yet increasing the size, length, and complexity of clinical trials is not an economically sustainable option and places further burdens on the ability of researchers to enroll and conduct clinical trials feasibly.

Rather, we should pursue approaches that more closely integrate reasonably sized pre-market clinical studies and real-world data with mandatory post-market surveillance and analysis of additional real-world data to assess safety and efficacy further and to refine the therapy's benefit/risk profile. For example, marketing approval should be granted on the basis of a demonstration of safety and efficacy in a highly targeted patient population (that would require fewer patients in clinical trials) with analysis of electronic health record data and "virtual" clinical studies in a post-market setting to support expanded indications.

6. ***As a Member of Congress, we hear tales about how companies meet with FDA on drug approval, and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science?***

The scientific method does not operate in a vacuum, and it is critical to promote the appropriate exchange of ideas and scientific learnings between academia, the private sector, and government. During drug development, sponsors often have difficulty communicating with their FDA review divisions outside of written exchanges of letters or formally scheduled meetings. Informal scientific dialogue can play an important role in understanding FDA expectations and ensuring that medical officers are aware of the underlying science supporting an investigational product.

Further, sequestration and recent budgetary restrictions have prevented FDA medical officers from attending scientific conferences and technical meetings. This has hindered the Agency's ability to keep pace with the rapid advancements in basic and applied research. We ask Congress to ensure that the Agency has adequate funding for professional development activities, scientific and technical capacity building, and scientific leadership.

The Honorable Jan Schakowsky

1. ***A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new Hepatitis C dn1g treatment costs about $100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation?***

As a representative of the leaders in the biopharmaceutical space, BIO is focused on policies that enhance the development of lifesaving treatments and cures, and ensuring patient access to them. Due to the expansions in the Affordable Care Act (ACA), more patients have the insurance they need to help them access care. Unfortunately, those benefits are increasingly characterized by narrow provider networks and higher cost sharing that undermines the very mission those insurance expansions were intended to meet. That's why biopharmaceutical innovators provide or support patient assistance programs to help patients gain access to needed therapies, either when they are uninsured or when their

insurance coverage has fallen short of their needs. Allowing innovators to continue to offer these programs is a critical component of ensuring patient access where insurance has fallen short.

2. ***I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIH is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIH means to the pace of drug innovation? How has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?***

Basic research begins and underpins the process of discovery. The importance of having a sustained federal commitment to funding basic research cannot be overstated. Federally-supported biomedical research builds the foundation of scientific and clinical knowledge that is widely communicated and used to improve the development of diagnostics, treatments, and cures.

The federal government funds biomedical research in the United States primarily through the NIH. The NIH is the nation's premier biomedical research agency and there is no private sector alternative for much of the basic research that NIH supports. NIH-supported research advances our knowledge about diseases and paves the way for the biopharmaceutical industry to develop the next generation of medicine therapies. However, after nearly a decade of budgets below biomedical inflation, NIH's inflation-adjusted funding is close to 20 percent lower today than in FY 2003. Decreasing investments in biomedical research will have long-term impacts, because making scientific discoveries and developing those discoveries into treatments and therapies that will improve the lives of patients is a long and difficult process that requires sustained commitment and investment.

This collaborative ecosystem also serves to create numerous direct jobs within the companies themselves as well as the indirect job creation with the numerous laboratories and suppliers contracted by the companies. As Alexis Borisy, Partner, ThirdRock Ventures, a leading investor in disruptive early stage companies, stated during his testimony before the Energy and Commerce Health Subcommittee on June 11th:

> *"Research dollars provided by the National Institutes of Health to universities and colleges throughout the country also serve to train future scientists for 21st century jobs. Currently, the U.S. biomedical research sector supports over 5 million high-paying jobs in the United States and has tremendous potential for growth. 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."*

Congress must focus on how to increase the NIH budget appropriately on an annual basis. Without such an annual increase, the budget and NIH's ability to fund meritorious research effectively and at a level that advances innovation declines with the inevitable increases in the cost of research. Ensuring that NIH is well-funded is necessary to sustain the public-

private collaboration that is transforming biomedical discoveries into innovative treatments for patients. Furthermore, efficiencies in NIH processes could lead to cost savings.

Consideration also could be given to how public-private partnerships might help. Increasing private funding for government-sponsored basic and applied research would require discussion of how to incentivize such funding and how such funding would be administered. It would be important, for any such funding from for-profit sources, to determine how a system could be structured to prevent either the appearance of or actual conflict of interest.

The Honorable H. Morgan Griffith

1. ***What legal barriers currently exist that limit the potential for doctors, researchers and drug companies to communicate on how therapies are working for patients in the real world? What can we do to break down some of those legal barriers that are preventing reasonable and valuable treatments from getting to patients?***

Broadly, FDA interpretation of current law and regulation limits a manufacturer's proactive communication about its product. Specifically, proactive manufacturer communication is generally restricted by FDA only to the information contained in the product label. The labeling includes the product indications for use approved by FDA, and product labeling is prohibited from listing any use that has not been approved by FDA. The FDA, of course, does not regulate the practice of medicine, and once a product is introduced, medical practice begins its iterative process, and scientific experience and knowledge may outpace the approved product labeling. Off label uses of biopharmaceutical products, based on practitioner real world experience with a product, are common, and recognized as having a societal benefit.

Nonetheless, proactive communication by a manufacturer of information about the use of a product that is not contained in the product label may be viewed as "off label promotion," and subject to significant enforcement efforts. This limitation affects even communication by a manufacturer of truthful and not misleading medical or scientific information with practitioners about the real world use of manufacturers' products. Manufacturers may not share information and participate in the iterative scientific and medical dialogue about their products on a proactive basis, instead only being permitted to do so reactively with various interpretive FDA restraints. Such approaches hinder the various users of medicines from easy access to information that can help them understand the range of treatment options for various conditions and impede the most effective use of certain medicines.

In addition, current law deals with the important question of providing payers and others with meaningful information regarding the pharmacoeconomic benefits of medicines. Specifically, Section 114 of the *Food and Drug Administration Modernization Act of 1997* (FDAMA) permits communication of pharmacoeconomic information to formulary committees and similar entities only if the information is directly related to an approved indication. This has undermined innovators' ability to meet requests for such information, which is increasingly demanded if our healthcare system is to evolve to one based on patient-centered outcomes and "value".

Broadly, the provision of truthful and non-misleading information to providers, payers, and patients about real world evidence and uses should not be impeded by unnecessary and cumbersome regulatory restrictions or requirements.

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June 10, 2014

Mr. Frank J. Sasinowski
Director
Hyman, Phelps & McNamara
700 13th Street, N.W., Suite 1200
Washington, D.C. 20005

Dear Mr. Sasinowski:

Thank you for appearing before the Subcommittee on Health on Tuesday, May 20, 2014, to testify at the hearing entitled "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Tuesday, June 24, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

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June 24, 2014

BY E-MAIL

Sydne Harwick
Sydne.Harwick@mail.house.gov

Dear Ms. Harwick:

I have provided responses to the questions for the record provided by the Members of the Energy and Commerce Subcommittee on Health regarding my testimony for the hearing entitled, "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation" held on Tuesday, May 20, 2014.

Please let me know if you have any questions or concerns related to the responses I am submitting.

Sincerely,

Frank J. Sasinowski

Director
Hyman, Phelps & McNamara, P.C.

Director
National Organization of Rare Disorders

The Honorable Gus Bilirakis

1. One mechanism drug companies have to improve certainty about the Agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract?

Yes, in the context of orphan drug development for rare diseases, SPA agreements have allowed the FDA and Sponsors to discuss and gain concurrence prospectively on protocol design and statistical issues, which has yielded greater certainty in drug development. Successful clinical trials for Americans with rare diseases have resulted from SPA agreements in which FDA has demonstrated considerable flexibility in clinical trial design, including subjects to be enrolled, section of endpoints, duration of trial and safety information to be collected.

2. For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate endpoints that are reasonably likely to predict a clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can FDA work with stakeholders to determine new endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?

From my observations, FDA works closely with both Academic and Industry Sponsors to determine appropriate new surrogate endpoints, such as seen in FDA's collaboration with the Critical Path Institute and its Industry partners on new surrogates. Furthermore, FDA has provided additional guidance to sponsors in its recently released final guidance, titled, "Expedited Programs for Serious Conditions – Drugs and Biologics." Section VII.C. of the guidance, titled "Evidentiary Criteria for Accelerated Approval," describes several factors FDA weighs in assessing whether the available evidence is sufficient to allow the Agency to conclude the proposed surrogate endpoint is reasonably likely to predict clinical benefit. In an analysis I conducted along with my colleague Alexander Varond, in which we looked at each of the 19 Subpart H approvals (that are not for AIDS or cancer), we found that FDA has shown great flexibility in applying its Accelerated Approval standards to therapies for serious diseases under FDA's review. *See* Comment of Hyman, Phelps & McNamara, P.C., Docket No. FDA-2013-D-0575 (Aug. 26, 2013), *available at* http://www.hpm.com/pdf/blog/Subpart%20H%20Analysis%20-%20FDA-2013-D-0575.pdf.

3. What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?

No comment. I am not an expert in post-approval outcomes data.

4. Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leveraged for supplemental applications?

There are benefits as well as limitations in using real word data in supplemental applications. In particular, when the real world data mirrors the already approved dosage in a similar population (e.g., gender, age, health status), then the observed safety outcomes can be useful in providing information that may confirm the safety profile of the drug as it is known for the approved indication or use. However, with regard to establishing evidence of efficacy, real world data will often lack sufficient methodological rigor to be of great value in advancing our understanding of the effectiveness of therapy (see 21 C.F.R. 314.126, the regulation that describes the conditions needed to have an adequate and controlled study). If, however, by "real world," the question is referring to studies that would be considered adequate and well controlled but just not conducted pursuant to a commercial Sponsor's investigational new drug (IND) exemption, then such "real world" data may be leveraged for both supporting the safety and effectiveness of the drug for the new use in a supplemental application. I have been involved with a number of instances, including one in which a patient advocacy organization, the LAM Foundation, had a major hand in designing and analyzing a study of an already approved drug, sirolimus, for another use: to treat women with LAM. This was a rigorous trial and its results were published in the New England Journal of Medicine and touted by the editors of the journal as a shining example of a patient organization leveraging an existing approved drug for a new use. *See* Francis McCormack et al., *Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis*, 364 N. Engl. J. Med. 1595 (2011); *see also* Julie Ingelfinder & Jeffrey Drazen, *Patient Organizations and Research on Rare Diseases*, 364 N. Engl. J. Med. 1670 (2011).

5. As a Member of Congress, we hear tales about how companies meet with FDA on drug approval, and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in

a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science?

Ensuring that FDA review staff are knowledgeable about the latest science is very important. From my experience in the rare disease space, it is not uncommon that FDA may not have an in-house medical reviewer with expertise in a particular rare disease or maybe who has ever even seen a patient with a particular rare condition since such conditions may be very rare. In these situations, Sponsors will often bring a rare disease medical expert to meet with the FDA, making them available to FDA to answer questions from their experience. Additionally, FDA will consult directly with rare disease medical experts and rare disease patient advocates to get input on complex issues, such as the risks and benefits of potential therapies, the design of clinical trials, and medical needs not met by existing therapies. NORD has been a proponent of this type of expert consultation, and along with the Cystic Fibrosis Foundation, was a champion of the Expanding and Promoting Expertise in Review of Rare Treatments (EXPERRT) Act that was included in the Food and Drug Administration Safety and Innovation Act (FDASIA), which reinforces and expands FDA access to rare disease experts.

The Honorable Jan Schakowsky

1. A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new Hepatitis C drug treatment costs about $100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation?

While I am not an expert in drug reimbursement, programs such as NORD's Patient Assistance Programs provide financial assistance with insurance premiums and co-pay fees, as well as assistance with reasonable and appropriate diagnostic testing expenses and travel to and consultation with disease specialists that are not covered by a patient's insurance plan. NORD also hosts a number of medication- and disease-specific assistance programs. *See* NORD's Patient Assistance Programs, *available at* https://www.rarediseases.org/patients-and-families/patient-assistance. This type of program, run by a non-profit patient advocacy organization, provides a trusted, neutral venue for patients with financial need to gain assistance. Unfortunately, NORD has been told by Sponsors that for-profit companies may be setting-up and operating shell so-called "non-profit" organizations to benefit from the operating revenue of Patient Assistance Programs. This siphons money from legitimate patient advocacy organizations that use Patient Advocacy Programs as a way to help patients and generate

much needed operating revenue. Meanwhile, these third-party operated programs do not provide the comfort of neutrality and reassurance that the program is operating in the best interest of the patient, which is crucial to protect vulnerable patients in need of assistance. The Subcommittee can provide leadership in further defining legitimate patient advocacy and other non-profit advocacy organizations to prevent this perversion of the system. The Subcommittee can also provide authorization for funding, as well as provide support for sponsor funding, to qualified patient advocacy organizations to host Patient Assistance Programs.

2. I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIH is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIFI means to the pace of drug innovation? Flow has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?

Thank you for your important testimony. Your testimony makes clear the harm caused by inadequately funding the NIH. I hope that we can work together to ensure that NIH has the resources it needs to ensure that we remain the world's leader in innovation and that we accelerate our ability to discover new treatments and cures that save lives and improve health.

I concur, and NORD has advocated, that the National Institutes of Health (NIH)'s funding for basic research, as well as translational research, has helped facilitate the development of new, innovative therapies for patients. I would not disagree that a reduction in inflation-adjusted funding would be a detriment to our biomedical research capacity. I would like to mention the need for increased appropriations for the Orphan Products Grants Program administered by the FDA Office of Orphan Products Development. This federally funded program provides grants to academic researchers and industry for pivotal clinical trials on new orphan drugs, medical devices, and medical foods for rare diseases. The Orphan Products Grants Program began in 1983 with a modest appropriate of $500,000 and has seen increases in the appropriation to the current $14-15 million (even though its authorization is for up to $25 million). Funding for this has remained constant at that level since 2005 with a decrease as a result of sequestration.

When inflation is taken into account, the program has actually only risen to about $6 million in 1982 dollars. Despite the relatively low levels of funding, the program has truly made a difference in the lives of patients, with about 10% of all therapies approved by FDA for Americans with rare diseases have received funding by the Orphan Products Grants Program. Given the extremely modest funds provided by taxpayers to this program, this return on taxpayers' investment (ROI) is highly remarkable! While FDASIA reauthorized grant funding for the Orphan Products Grants Program, increasing future funding will allow additional studies in conditions in vulnerable and difficult-to-treat populations, as well as those that have no available options.

The Honorable H. Morgan Griffith

1. What legal barriers currently exist that limit the potential for doctors, researchers and drug companies to communicate on how therapies are working for patients in the real world? What can we do to break down some of those legal barriers that are preventing reasonable and valuable treatments from getting to the patients?

At the May 20th hearing, I stated that I was (and still am) unaware of what state and federal legal barriers may exist that impede the conduct of natural history studies and patient registries, but I repeat here how critical it is for developing new innovative therapies for Americans with rare diseases that our legal systems not slow or halt natural history studies and patient registries. Patient registries are a cost-effective instrument for increasing knowledge of a disease, for supporting fundamental clinical and epidemiological research, and for conducting post-marketing surveillance of drugs. Natural history studies are an important tool for understanding the etiology of a disease, its range of phenotypic manifestations, and its relative rate of progression, all of which can support identification of biomarkers and surrogates as well as innovative study design, which collectively advance drug development As I mentioned in my remarks at the hearing, if we understand more about the natural history or progression of a disease, we will be better able to discern what is the treatment benefit of a novel therapy versus what is the natural course of the disease. Similarly, we could tell what is a safety signal that is due to the therapy rather than a signal that is part of the natural course of the progression of the disease. Therefore, encouraging the development of natural history studies and patient registries in every disease is very important. Congressional support for these critical tools would be vital to securing the aid of medical professionals and institutions in gathering information in a consistent, uniform manner and sharing such information for the benefit of patients and drug development.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

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June 10, 2014

Dr. Jeff Allen
Executive Director
Friends of Cancer Research
1800 M Street, N.W., Suite 1050 South
Washington, D.C. 20036

Dear Dr. Allen:

Thank you for appearing before the Subcommittee on Health on Tuesday, May 20, 2014, to testify at the hearing entitled "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

The Honorable Gus Bilirakis

1. **One mechanism drug companies have to improve certainty about the Agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract.**

Special Protocol Assessments (SPAs) are agreements between the FDA and trial sponsors regarding the protocol design, size, and endpoints of a particular trial. SPAs are desirable because they provide sponsors with increased confidence that the FDA is satisfied with the design and execution of a trial, and can ensure that sponsors receive a timely response to questions that they may have during the development of a new product. However, the FDA does have the right to rescind a SPA if public health concerns become evident that were not recognized at the time the SPA was reached. It is up to trial sponsors to disclose publicly whether they have obtained a SPA agreement with the FDA, so not all such agreements are known. The FDA does release the number of requests for SPAs it receives.

Requests to FDA for SPAs[1]

Year	2008	2009	2010	2011	2012	2013
# of SPA Requests	354	336	309	313	288	220

An analysis conducted by the market research firm PROPTHINK concluded that "sponsors who have successfully conducted studies that have met the predefined outcomes in a SPA agreement are highly unlikely to be rejected on the grounds that more clinical data/studies are required." In addition, the analysis noted that "a successful SPA-backed NDA does not guarantee approval on the first regulatory review cycle."[2] Thus, SPAs increase the likelihood that the FDA will evaluate efficacy and safety data without raising objections to elements of trial design, but that does not guarantee that the efficacy and safety data will be robust enough to support approval.

In the field of cancer, there are several examples of drugs receiving SPAs and being subsequently approved: Onyx Pharmaceuticals' Kyprolis for multiple myeloma received a SPA in 2010 and was approved in 2012; Abraxis' Abraxane for non-small cell lung cancer received a SPA in 2007 and was approved in 2012; Gloucester's Istodax for a rare lymphoma received a SPA in 2007 and was approved in 2009; Seattle Genetics' Adcetris for Hodgkin lymphoma received a SPA in 2010 and was approved in 2011.

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[1] FDA Prescription Drug User Fee FY2013 Performance Report: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384035.pdf Accessed 6/12/14

[2] Special Protocol Assessments: The Case Studies: https://propthink.com/special-protocol-assessments-a-case-study/ Feb 22, 2013. Accessed 6/12/14

An example of a drug that received a SPA but was not approved due to an unfavorable risk/benefit profile was Ariad's ridaforolimus for soft tissue sarcoma. In this case, even with the confidence from the FDA in the trial design, during further testing the drug was shown to have significant risk for kidney and heart problems, with marginal potential benefit.

2. **For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate endpoints that are reasonably likely to predict clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can the FDA work with stakeholders to determine new endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?**

Accelerated Approval, as codified in the 2012 FDA Safety and Innovation Act, is the approval of a drug based upon its effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.[3] It has been an extremely useful tool for the FDA to bring therapies to patients for serious conditions, as has shown especially instrumental in looking at therapies that treat HIV and different forms of cancer.[4] While it is a requirement for a drug approved under Accelerated Approval to treat a serious or life-threatening illness, a key reason that Accelerated Approval has been used more frequently in the cases of HIV and cancers is due to the availability of surrogate endpoints that have been demonstrated to be likely to predict a clinical benefit – such as viral load reduction and tumor shrinkage, respectfully. Conversely, there are other disease settings where an endpoint other than overall survival has been so clearly correlated to clinical benefit that it would no longer be characterized as a surrogate, and full approval could be granted based upon a favorable improvement to that endpoint measure (without the post-market commitments of an Accelerated Approval). An example of this is a drug effect on lowering cholesterol in the blood as a predictor of improved heart health.

In all of those cases (cancer, HIV, heart disease) research on the intermediate endpoints was needed to help correlate the surrogate to positive clinical outcomes. FDA has historically encouraged new research to identify potential intermediate endpoints and recently developed programs such as the Biomarker Qualification program to help provide input from the agency into on-going research programs seeking to validate new endpoints.[5] The FDA is quite receptive to working with stakeholders interested in researching potential intermediate endpoints. Additional resources for the agency could help expand this work, since often times, due to funding and personnel constraints, advancing new regulatory programs are difficult to execute with the many significant core responsibilities of agency staff. A

[3] Food and Drug Administration Safety and Innovation Act PL 112-144 Sec. 901.
[4] Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst. 2011;103(8):636-44. Epub 2011/03/23. doi: 10.1093/jnci/djr062. PubMed PMID: 21422403
[5] FDA Biomarker Qualification Program: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm Accessed 6/13/14

coordinated effort by experts throughout biomedical research community could; help identify which endpoints in different diseases should be of the highest priority, collaborate with FDA to design the appropriate studies for attempting to correlate biomarker candidates to clinical outcomes, and focus resources toward conducting those studies.

3. **What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?**

Most medical records and health data collection systems were not set up to have research as a primary function. Instead, they were developed to process payment for services provided or to provide a record for a single person, at a specific office or center, without the intent or ability to aggregate data from a population standpoint. Some of these barriers have been reduce over time with the advancement of health IT and the implementation of new technology in different care settings or by different care providers and insurers. However, there are still numerous restrictions on how data can be collected and aggregated with privacy concerns frequently cited as a key barrier.

While misuse of data for discriminatory purposes is critical to prevent and patient privacy protections must remain vigilant especially as more data is being generated on each person today than ever before. This provides new opportunities for empowering people to be more active in their care, have access to their health information, and create ways in which research can be conducted in different ways without having to necessarily be a part of a clinical trial. For example, patient data no longer needs to only be collected during periodic doctor visits. Today, many consumers employ technologies to track their daily health for their own personal knowledge. This type of information, while perhaps not as rigorous as full medical exam, can provide longitudinal data about how a medical intervention may be affecting daily activity, provide a way for people to record their direct experience with a medication as its happening, and help optimize appropriate use of medication. Streamlining different technologies and developing ways for them to interact with a central, interoperable health record with the appropriate, but not unduly burdensome, privacy protections could create new ways for generating health data in the real world.

4. **Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leverage for supplemental applications?**

Collecting and utilizing data about a drug's effect in a disease setting outside of the initially approved indication is an important part understanding the full and optimal use of a drug. This can be done in the context of a formal clinical trial or through additional monitoring of off-label use of a drug. In some

cases of Accelerated Approval where a drug is granted an initial approval in one type of cancer and the required confirmatory studies are actually conducted in a different subset or type of cancer. Not only has this confirmed the initial studies of the drug, but it can lead to an expansion of the label and provide benefit to a broader group of patients. This is one confined example that would use a formal clinical trial as the data source for developing a growing body of evidence about a drug, but perhaps some common principles can be applied.

A major challenge in using real world data is collecting data for patients being treat with a therapy off-label. Registries are frequently established to collect specific information about the effect of a drug outside of a clinical trial. However, while registries are less resource intensive than a typical clinical trial, there are limitations to the conclusions that can be made based on observational data. It could be useful to prospectively work with a wide variety of stakeholders to define what data would need to be collected in the form of a registry that could facilitate a regulatory decision on the supplemental use of a drug. This would likely need to be evaluated on a case by case basis, but it could be an available option for expanding the use of a drug in some cases, particularly when the safety profile of the drug is well understood.

While this could provide one option for generating additional data without the challenge of conducting a clinical trial after the drug has been on the market, it does not alleviate the challenge of tracking off-label use more generally without the proactive intent for expanding the label of the drug.

5. **As a Member of Congress, we hear tales about how companies meet with FDA on drug approval, and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science.**

Scientific advancements are occurring at increasingly rapid rate. In order to fully capitalize on prior investments in research and development, all components of the biomedical research enterprise need to keep pace or they otherwise risk becoming a limiting step that could slow progress in health care. Like any physician is expected to keep up on the latest advances in science so they can treat their patients with the most effective therapies, FDA scientific review staff needs to continually learn about and be involved in cutting edge science. The FDA's current budget often times hinders this vital education from occurring, which could leave the FDA a step behind the science. One example of this is limited travel budgets for agency officials to participate in scientific meetings. Annual meetings of professional societies and other significant conferences that address key issues among the regulatory and scientific communities provide venues for the most recent scientific and clinical advancements to be presented and discussed. If FDA officials are to advise on the development and review marketing applications regarding the most advanced scientific discoveries they need to be involved in the robust scientific discussions and debates that facilitate their development.

The Honorable Jan Schakowsky

1. **A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new Hepatitis C drug treatment costs about $100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation**

Advancements in medicine and the development of new drugs won't achieve their intended benefit if patients can't access them. The passage and implementation of the Affordable Care Act is provides the opportunity for millions of Americans that previous had no health insurance to obtain coverage. The terms of coverage and the benefits that it provides will continue to be examined as the exchanges expand enrollment, and states adapt to this new law. It will be important to look a variety of factors that still may impede access to such transformational treatments. For example, if the co-pays associated with specialty drugs like those associated with treating illnesses like Hepatitis C, results in a patient out-of-pocket cost so high that it is causing significant limitations for people that need these drugs, then re-examining cost sharing structures may be necessary. This is a different issue than the proposed base price of the drug, but it may be an actual point where access is limited. Whether a drug costs $100,000 per year or is reduced by ¼ to $75,000 per year, if the co-pay originally associated with it was unaffordable to the patients it's likely that the co-pay will remain a barrier to access regardless of the price of the drug. Price negotiations, like those that take place between private sector payers, VA hospitals, and others, but not between CMS and companies, could be further evaluated.

This is just one example of how shared cost structures may need to be examined. It is not meant to be rationale for any unjustified pricing, but rather an acknowledgement that realistic out-of-pocket costs and cost sharing strategies may need to be examined, and that all stakeholders are going to have to play a part to ensure that patients have access to new medicines that can improve their lives.

2. **Advocates often work with Members of Congress to request that FDA develop Guidance Documents in an effort to spur discovery and innovation for various diseases. Would you discuss the importance of Guidance Documents to accelerating the drug development process? In your opinion, is the FDA doing a sufficient job in developing Guidance Documents? What can Congress do to increase the production of these important documents?**

FDA Guidance documents provide the research community with up to date information about agency requirements, current policies, and potential approaches to drug development. While many decisions need to be handled on a case by case basis, these documents provide a framework for establishing the

different parts of a drug development and research program and help inform future interactions with the FDA. Specifically, FDA has used guidance documents as a way to effectively communicate with researchers and companies about new strategies for drug development such as co-developing a drug with a companion diagnostic[6], use of novel endpoints like pathologic complete response in breast cancer[7], or developing novel combinations of drugs to treat serious illnesses.[8]

FDA's ability to develop new guidance documents are limited by resources, time, and available personnel. Under these circumstances, FDA has been consistent in issuing Guidance documents from year to year, but with additional resources more Guidance documents could be developed, and with increased ability to interact with experts across the biomedical research community, more robust and forward-thinking guidance could be developed [9] Congress should increase the base funding for FDA to give the agency a greater ability to prioritize the development of Guidance documents, many of which may be outside the scope of programs to which user fees are able to be applied. Establishing a process that would allow external input regarding potential subjects for future guidance documents could also be a helpful way of ensuring that FDA fully realizes the components of drug development that researchers are challenged by most and identify areas where additional guidance documents may be useful.

3. **I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIG is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIH means to the pace of drug innovation? How has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?**

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[6] FDA Guidance: In Vitro Companion Diagnostic Devices. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf Accessed 6/19/14

[7] FDA Guidance: Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf Accessed 6/19/14

[8] FDA Guidance: Codevelopment of Two or More New Investigational Drugs for Use in Combination: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf Accessed 6/19/14

[9] FDA Drugs (Guidances): http://www.fda.gov/Drugs/GuidancecomplianceRegulatoryInformation/Guidances/default.htm Accessed 6/19/14

Thank you for your on-going and steadfast support for funding of biomedical sciences and NIH, it is greatly appreciated. Without champions for research like you much of the progress that has been made to date would not have occurred.

NIH funding is the engine that drives discovery and a key reason that we are currently seeing many scientific advances today. However, as you described over all purchasing power continues to decline. This has the ability to slow the pace of innovation because it simply will take longer to conduct the many potentially transformative research projects that will have to be postponed until funding becomes available. One example in cancer is an NCI initiative called The Cancer Genome Atlas (TCGA). Since the project began in DATE, about 30 different tumor types have been gnomically sequenced to provide cutting-edge information about cellular alterations that may be driving cancerous growth in those tumors.[10] With additional resources, more tumor types could be analyzed. The results of these advanced analyses help to identify targets that drugs can be designed toward and potentially stop the cancerous growth. These early studies serve as the foundation for innovative drug development and projects like the Lung-MAP trial, a public private partnership that we spearheaded this past week that will simultaneously test multiple drugs that are targeted toward different molecular alterations.[11] Lung-MAP is designed to address several current challenges in clinical trials and has the ability to improve enrollment, enhance consistency, increase efficiency, reduce costs, and most importantly - improve patients' lives. The design of Lung-MAP utilized the results of TGCA analysis of squamous cell lung cancer. This example of accelerating the pace of innovative drug development could not occur without the strong foundation of knowledge only possible through robust NIH funding. Continued erosion to NIH purchasing power will limit the number and delay the pace at which these stepwise research projects can be conducted, leaving patients to wait for potentially life improving products stuck in the pipeline.

In addition to the direct consequence in delayed development, reduced purchasing power brings long term damage to the biomedical research enterprise. Decreased purchasing power has caused a reduction of scientists that are able to continue their careers in research. Perhaps more detrimental is that has discouraged young talent from considering research as a viable career option and forced them to focus their talents into other fields. The average length of time from graduating high school to completing a doctorate degree in the life science is approximately 11 years (for students that go directly from a bachelors program through doctorate).[12] If the number of young scientists going into life sciences declines, even if NIH funding were to be restored to prior levels of purchasing power, it will take over a decade to reverse the trend in a diminished workforce to develop new medicines.

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[10] National Cancer Institute, The Cancer Genome Atlas: http://cancergenome.nih.gov/cancersselected Accessed 6/19/14

[11] Lung-MAP: http://www.lung-map.org/ Accessed 6/19/14

[12] National Science Foundation, Higher Education in Science and Engineering: http://www.nsf.gov/statistics/seind12/c2/c2s3.htm Accessed 6/19/14

The Honorable H. Morgan Griffith

1. **What legal barriers currently exist that limit the potential for doctors, researchers and drug companies to communicate on how therapies are working for patients in the real world? What can we do to break down some of those legal barriers that are preventing reasonable and valuable treatments from getting to the patient?**

Due to advanced information systems, more data is being generated in healthcare than ever before. This presents new opportunities for improved learning about outcomes on a broad population level and for developing new methods for conducting research. The Health Insurance Portability and Accountability Act was passed in 1996 to protect patient privacy regarding health records. It has yielded important steps to help protect privacy and raise awareness about the need for privacy measures. However, in today's growing electronically-based systems it may present barriers to fully capitalizing on research using data generated in healthcare. The existing privacy rules can prevent researcher from accessing large numbers of patient records to evaluate the safety and efficacy of new drugs outside of clinical trials or to conduct other research activities, such as assessing long term data about different interventions.

In the case which is drug is being used in an off-label setting, companies are restricted from communicating any benefits associated with its use to prevent general promotion of drug for uses other than those for which they are FDA approved. While these restrictions were put into place to help prevent misinformation reaching consumers, there are situations where emerging characteristics of a drug have been made clear through real world use of a product and that information may not be formally put into the label. In a non-promotional way, consumers could benefit from knowing additional information about a drug they're considering or already taking before having to wait for a formal label updating process before the information can be communicated.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
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ONE HUNDRED THIRTEENTH CONGRESS

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June 10, 2014

Dr. Sean Tunis
Founder and CEO
Center for Medical Technology Policy
World Trade Center Baltimore
401 East Pratt Street, Suite 631
Baltimore, MD 21202

Dear Dr. Tunis:

Thank you for appearing before the Subcommittee on Health on Tuesday, May 20, 2014, to testify at the hearing entitled "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Tuesday, June 24, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments