American Psychiatric Association

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June 9th, 2014

The Honorable Fred Upton
Chairman, Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn H.O.B.
Washington, D.C. 20515

The Honorable Diana DeGette
U.S. House of Representatives
2368 Rayburn H.O.B.
Washington, D.C. 20515

Dear Chairman Upton and Representative DeGette,

On behalf of the American Psychiatric Association (APA), the medical specialty society representing more than 35,000 psychiatric physicians and their patients, we thank you for your leadership in organizing the 21st Century Cures Initiative. APA is deeply invested in the importance of promoting research on mental illnesses and substance use disorders in order to identify and utilize the 21st century treatments for our patients. Remedying regulatory barriers to improve medical innovation and treatment for mental illnesses and substance use disorders is critical to the future of psychiatric research. APA appreciates this opportunity to be a resource to your committee.

Our patients and their families need access to a range of treatment options and deserve to experience the promise of future psychopharmacological breakthroughs. While medications have been developed to address the symptoms of serious mental illnesses and substance use disorders, no cures have yet been identified. Medications, as part of a comprehensive treatment plan, can make the difference between an active life in the community and reliance on caretakers and income supports. The side effects of medications can be difficult for some patients to manage and still others may not adequately respond to currently available treatments.

The reduction of federal and private investment in psychiatric medications is greatly concerning. For the past five years, the National Institutes of Health's appropriations have not kept pace with biomedical inflation. Sequestration has further eroded the

NIH's ability to fund new research opportunities and develop the careers of young biomedical researchers. Private investment in psychiatric research and innovation has waned due to regulatory uncertainty, length of time to bring treatments to market, and the intrinsic complexity of psychiatric disorders, among other reasons.

Scope of Mental Illness and Substance Use Disorders

The prevalence of serious mental illness and substance use disorders is staggering. The National Institute of Mental Health (NIMH) conservatively estimates the total costs associated with serious mental illnesses, those disorders that are severely debilitating and affect about 6 percent of the adult population, to be in excess of $300 billion per year including $193 billion in loss of earnings, $100 billion in heath care expenditures, and $24.3 billion in disability benefits. The costs associated with mental illness stem from both the direct expenditures for mental health services and treatment (direct costs) and from expenditures and losses related to the disability caused by these disorders (indirect costs). Indirect costs include public expenditures for disability support and lost earnings among people with serious mental illness. More specific diagnostic tools, treatments with fewer side effects, and the potential of genomic-sensitive treatments should be research priorities for both government and industry. Investigating the important differences that occur in patterns of mental illness/mental health care services use between genders, and among ethnic minorities, is another priority that must be emphasized. For example, gender and ethnic differences exist in the development, clinical course, and treatment outcomes of bipolar disorder and schizophrenia. We need to understand the reasons for these disparities and develop methods of addressing them.

Substance use disorders (SUDs) have strikingly negative consequences for individuals, families and society. Estimates of the total overall costs of SUDs in the United States, including productivity plus health and crime related costs exceed $600 billion annually. This includes approximately $181 billion for illicit drugs, $193 billion for tobacco, and $235 billion for alcohol. As staggering as these numbers are, they do not fully describe the breadth of destructive public health and safety implications of drug abuse and addiction such as family disintegration, loss of employment, failure in school, domestic violence, and child abuse. The National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) are tasked with developing and implementing new treatments for addiction and identifying the causes and contributors of addiction. The need has never been greater for the development of novel, non-opioid medications to manage pain and for treatments that ameliorate the impact of alcohol on liver disease.

An analysis by Milliman for the APA showed that patients with mental health and substance use disorder use almost $292 billion of health care services more per year than those without these disorders, the vast majority for increased general medical services. When paired with the known early mortality of those with mental health and substance use illness these disorders need substantial research investment.

Recommendations

APA urges sustained, robust funding for biomedical research given the heavy medical and economic burden of mental and subsistence use disorders. Attention must also be paid to improve the delivery of evidence-based treatments in the changing health care landscape. In March 2013, the American Psychiatric Foundation convened a "Pipeline Summit" that included researchers, patient groups, biomedical investors and federal government representatives who discussed ways to remedy the shrinking pipeline for psychiatric medications. The meeting encompassed all aspects of research and identified several potential regulatory improvements which could speed medical innovation. These included:

- Improve data sharing mechanisms between researchers and industry in pre-competitive collaboration in order to speed target identification and validation, identify biomarkers and standardize clinical trial protocols including common benchmarks for meaningful effect sizes in clinical trials.
- Improve industry and federal research collaborations. For example, jointly maintaining a voluntary registry of people living with schizophrenia to provide longitudinal information of symptom manifestation and potentially identify patients for clinical trials.
- Speed the development of a neuroscience community data sharing portal at the Food and Drug Administration (FDA) to establish a clinical trials registry for psychiatric investigation. A clinical trials registry would allow for systemic evaluations of failed trials which in turn would better inform subsequent research designs.
- Explore incentives for investment such as market exclusivity for "first in class" novel medications, patent extensions and data package protections. Modest extensions could provide companies more predictability in the regulatory approval proves. More predictability may encourage investors to invest in psychiatric research. Any patent incentives would have to be balanced with the needs of patients.

Current Regulatory Efforts

APA is encouraged by recent federally-led efforts to improve the regulatory environment to strengthen research collaboration including the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the National Center for Advancing Translational Sciences (NCATS).

The BRAIN Initiative promises significant breakthroughs to treat neurological diseases, including mental illness and substance use disorders, which require technological innovations to develop new ways of mapping neurological pathways. The BRAIN Initiative began in 2014 and will yield tremendous advances in understanding the foundations and future of neurosciences. The BRAIN Initiative's three federal funding agencies, NIH, National Science Foundation (NSF) and Defense Advanced Research Projects Agency (DARPA), are collaborating with private organizations to leverage advances in nanoscience, imaging, engineering and informatics. The coordination of scientific advances for a common purpose – improving psychiatric research tools -- will accelerate the development of better diagnostics and treatments for brain ailments. The inclusion of improved identification neural circuitry and genetic markers are important

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APA is encouraged by bipartisan interest in authorizing additional funding for NIMH to study the causes and potential treatments for self and other directed violence as well as the BRAIN Initiative. This effort is promoted by Representative Tim Murphy in his Helping Families in Mental Health Crisis Act (H.R. 3717) and included in Representative Ron Barber's Strengthening Mental Health in Our Communities Act (H.R. 4574). It is APA's hope that bipartisan recognition of the need to fund psychiatric research will translate into bipartisan action to enact additional funding to support these critically needed activities within NIMH.

Thank you for the opportunity to share APA's recommendations to ameliorate regulatory barriers to medical innovations and support the federal investments necessary to identify and utilize 21st century cures. APA is happy to be a resource for psychiatric research expertise and we look forward to working with you as the Committee's investigation continues.

Sincerely,

Paul Summergrad, M.D.
President

Saul Levin, M.D., M.P.A.
CEO and Medical Director

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Comments by the American Society for Biochemistry and Molecular Biology to the Energy and Commerce Committee
Request for Comments on "*21st Century Cures: A Call to Action*"
May 30, 2014

The vibrant culture of freedom and curiosity that abounds in the United States' scientific research enterprise has produced astounding breakthroughs in every field of science, from astrophysics to zoology. Specifically, federal investments in biomedical research through the National Institutes of Health, the National Science Foundation, the Food and Drug Administration and others, have resulted in a steadily increasing life expectancy for Americans. From the invention of vaccines and the prevention of myriad diseases to the most recent advances in molecular medicine, federally funded biomedical research saves lives.

However, today's biomedical research enterprise is out of balance, placing the U.S. at risk of losing its position as the global leader in biomedical innovation. The major stakeholders in the biomedical research enterprise—government, academia and industry—each face serious challenges that must be addressed to keep the U.S. at the forefront of research. The federal investment in science has faltered over the past decade, and federal regulations slow the pace with which discoveries are made and translated to beneficial products. Improvements in academic Ph.D. training programs are necessary to prepare young scientists for the current job market and to enhance collaborations with the other stakeholders. And an industry that is more transparent with regard to experimental results and funding strategies will allow for an alignment of research goals among all stakeholders. Together, academia, government and industry can make significant changes that will ensure that biomedical research remains an attractive career path for our most talented young people and ensures that the American research enterprise remains second-to-none in the world.

For some time, the Public Affairs Advisory Committee of the American Society of Biochemistry and Molecular Biology has been working on the issue of sustainability in biomedical research. In our view, a sustainable biomedical research enterprise should train the right number of scientists to fill the needs of the marketplace; have a sustainable and robust funding stream and enable government, academia and industry to work together in a more seamless fashion to improve the rate that discoveries are made and moved to the market. The ASBMB white paper on the SBRE was released in August 2013[1,2]. We also held a well attended panel discussion at a recent national meeting that brought together representatives from the different stakeholder groups to discuss the barriers to sustainability. Our next step will be to further delve into the issues facing each stakeholder and come to an agreement on how best to break down these barriers.

Because we ourselves are working hard to create a sustainable biomedical research enterprise, we are delighted that the U.S. House Energy and Commerce committee is also addressing the critical issues confronting biomedical research today. Biomedical research has a long history of bipartisan support, and we are pleased that this tradition has continued in the current activities of the Energy and Commerce committee. Below are the ASBMB's responses to several of the questions posed in the "21st Century Cures: A Call to Action" white paper.

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[1] Berg, Jeremy. "Imagining a sustainable biomedical enterprise." *ASBMB Today*. 2013. http://bit.ly/1n53mfn
[2] ASBMB Public Affairs Advisory Committee. "Toward a Sustainable Biomedical Research Enterprise." 2013. http://bit.ly/1n4GOel

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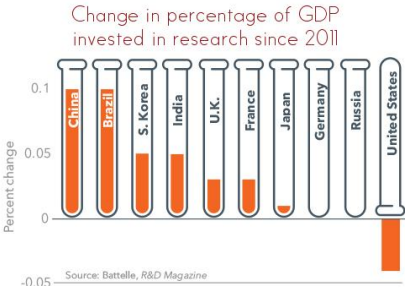
How can we make sure the U.S. maintains its leadership role in global research and discovery?

Biomedical research is now a global enterprise, and, despite our accomplishments, the U.S. is in danger of losing its dominance in this area of research.[3] Over the past three years, most countries have increased their investments in biomedical research, while the U.S. has reduced its investments. This trend threatens to cede the discoveries of tomorrow to up-and-coming scientific powerhouses in Europe and Asia.



Of the countries that invest in research, the United States is the only one to reduce their investment over the past three years.[3]

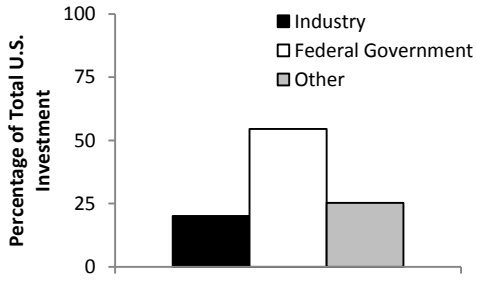
To ensure that the U.S. maintains its leadership role in global research and discovery, the federal government must commit to being the enduring foundational investor in basic biomedical research. Federal investment in basic research is the cornerstone of the entire enterprise. This investment has led to wonderful and beneficial discoveries that have improved human health while also improving our economy and higher education system to the point that people from all over the world come to the U.S. to study.

Basic research serves as the foundation for all other aspects of discovery and development. Thus, to remain the global leader in research and discovery, the federal government should maintain its bipartisan support of the research enterprise and commit to a plan that provides robust, predictable increases in funding for basic biomedical research. The first step of such a plan should increase the funding of the NIH to $32 billion and the NSF to $7.6 billion for fiscal 2015.

How much of the financial contribution for science come from public sources? Private? How can public-private partnerships further the discovery process?

Although basic research has always been a winning long-term investment, short-term outcomes are unpredictable. The freedom to fail and try again is an integral aspect of scientific exploration and is essential to the success of the research enterprise. The federal government is the only institution that is positioned to invest substantial capital in long-term, high-risk projects such as basic research, and it must therefore remain the enduring foundational investor in basic biomedical research.

Important investments in research are made by industrial and philanthropic organizations. Industry has always played a leading role in identifying promising therapeutics and developing them into useful products. The result is that industrial investments in research are short-term, risk-averse and bottom-line driven. Differences between federal and industrial investment strategies are evident in expenditure distributions: in 2011, industry funded 63 percent of all U.S. R&D, but this investment was focused on applied research and development. When it comes to basic research, the federal government provided 55 percent of the funding, underscoring the federal government's important role in the research enterprise.[4]



The federal government is the largest investor in U.S. basic research.[4]

[3] ASBMB. "Unlimited Potential, Vanishing Opportunity." 2013. http://bit.ly/1nXxAlH
[4] National Center for Science and Engineering Statistics. "Science and Engineering Indicators 2014." http://1.usa.gov/Sfx4UY

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Similarly, philanthropic investments in research, though critical, are often focused on development-ready, disease-focused research projects.

Enhancing the interactions among research enterprise stakeholders is one of the core tenets of the ASBMB's SBRE initiative. Despite their fundamentally different roles and investment strategies, improved partnerships between academic, industrial and governmental researchers are critical to maintaining and expanding the potential for discovery and development. One barrier to improved partnerships is the handling of intellectual property issues among those that invest in basic research. These negotiations often slow the technology transfer process, thereby delaying innovation and drug development.

To make an investment in basic research more attractive for private funding, these IP issues need to be addressed. While academia and industry have a reasonable mechanism for tech transfer, unifying tech transfer procedures across all university and company partnerships will reduce the time and cost associated with renegotiating every collaboration. Additionally, as noted by the President's Council of Advisors on Science and Technology, Congress and the administration can do more to improve tech transfer at the National Labs to speed the development and delivery of promising new discoveries to all Americans.[5] These reforms will forge closer ties among the stakeholders and allow for more private investment in basic research.

How can we harness our nation's desire, human capital, and technological know-how to get to the bottom of what may cause Alzheimer's and other deadly diseases or conditions? How can we incentivize, coordinate, and accelerate research for diseases or conditions we know relatively little about?

Scientific research is driven by questions about the natural world, and sometimes the answers to these questions reveal new directions and new phenomena that hold promise for disease treatments. Thus, research into basic biology or rare conditions may not initially appear to address larger societal needs, but the outcome of such research can and does profoundly affect many areas of research. For example, basic research into nematode movement uncovered a biological pathway that is used by almost all organisms to fight disease. This work garnered the Nobel Prize in Physiology or Medicine in 2006 and is now being exploited to fight a variety of human ailments including cancer. The outcomes of basic research will yield important information about diseases and strategies for treatments of many diseases, albeit often in unpredictable ways.

However, we must also ensure that we are conducting research into the many deadly and costly diseases that afflict humans. Industry has already taken the lead to develop treatments for these conditions. However, the fact that we do not yet have a treatment for Alzheimer's disease, for example, indicates the need for a closer partnership among all research enterprise stakeholders. One step toward these closer relationships is the NIH's Advancing Medicines Partnership project, which is a collaboration among academia, industry and government.[6] Many more stakeholder partnerships similar to the AMP will be required if we are to make advances on the serious diseases that afflict humans today.

[5] President's Council of Advisors on Science and Technology. "Transformation and Opportunity: The Future of the U.S. Research Enterprise." 2012. http://1.usa.gov/1nBkviF

[6] National Institutes of Health. "Accelerating Medicines Partnership." 2014. http://1.usa.gov/1eQrFYk

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The mechanism for researching and pursuing leads on these diseases is already in place. The NIH, NSF and others already have a robust system of peer review that evaluates and funds promising research into the underlying mechanisms of human biology and disease. Minimizing the boom-and-bust cycle of research funding, promoting closer relationships among stakeholders and improving the training of bright, young scientists will move the entire research enterprise onto a more sustainable path and resolve many of the issues that slow discovery, development and delivery of beneficial therapies and cures. A smoothly functioning enterprise will provide sufficient incentive to ensure that American researchers are making progress as fast and efficiently as possible.

How can we best leverage advances in translational research, health info tech, and communications so that we can collectively "connect the dots" more quickly and start developing potential therapies and cures?

One of the main goals of the ASBMB PAAC's work on establishing a SBRE is to identify the barriers that hinder interactions among academia, industry and government and come up with solutions to eliminate them. Whether they affect collaboration, tech transfer, clinical trials, intellectual property or other multi-stakeholder concerns, barriers slow the process which delays delivery of life saving treatments and cures to patients.

Industry, which does the majority of product development and testing, is often frustrated by the academic rules and bureaucracy regarding technology transfer while federal regulations regarding clinical trials and data sharing are so costly that only the most promising discoveries are even considered for development. Furthermore, an underfunded and understaffed FDA limits the speed with which new drugs and technologies can be brought to market. With the goals of ensuring patient safety and minimizing costs, each stakeholder should examine their role in the pipeline of discovery to determine the biggest hindrances to working together and work together to overcome them. Such cooperation could be a boon for researchers and patients. For example, with stakeholders working together to reduce the cost of clinical trials, companies will be able to invest more of their resources in developing discoveries made in academia and help make advances in regulatory science to enhance the government's ability to ensure the safety of new therapies and cures.

How are other countries attracting companies and investment? Should we adopt some of those policies? What else can we do to lead the way?

The country with the most innovative workforce will be the one that recruits and trains the most driven, creative and talented people from around the world and provides them with sufficient resources to achieve their dreams. The United States is still the global leader in this regard, primarily because we still have the best higher education system and an unsurpassed research infrastructure. To maintain this advantage, however, training programs must be updated to prepare students for the variety of careers available to them not only in academia, but also in government, industry and elsewhere. In addition, visa reform is needed so that we can retain the talented foreign scientists who train here, and allow them to make their groundbreaking discoveries here, to the benefit of all Americans.[7,8]

The current system provides excellent training in academic research. However, there is also a need to institute new programs that better train students for the variety of careers available to them outside of academia. This will benefit all of the stakeholders by reducing the time and money required to retrain

[7] ASBMB. "Unlimited Potential, Vanishing Opportunity." 2013. http://bit.ly/1nXxAlH
[8] Fritze, John. "U.S. cuts could lead to 'brain drain' in medicine." *The Baltimore Sun*. 2013. http://bit.ly/1tbmZ8R

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talented individuals to do a variety of different jobs. Furthermore, students with the skills to work outside of academia will serve as ambassadors from one stakeholder group to another, facilitating the movement of knowledge and technology. These reforms will keep the American training system the best in the world, and it will serve as a beacon to all scientists that the U.S. is the best place to conduct research.

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The ASBMB is a nonprofit scientific and educational organization that was established in 1906 by 28 biochemists and has since grown to an organization with more than 12,000 members worldwide. Most members conduct research and teach at colleges and universities, government laboratories, nonprofit research institutions and industry. We are proud to include 102 Nobel Prize winners among our members.

We are pleased that the Energy & Commerce committee is examining so many critical issues confronting the biomedical research enterprise today. We believe the entire enterprise must move in a direction of sustainability with regard to workforce, funding, and interactions among stakeholders. Ultimately, this will accelerate the rate of discovery and reduce the costs of the technology and drug development, all in a safe and effective manner that improves the health and economic well-being of Americans. The ASBMB and the Public Affairs Advisory Committee stand ready to help the Energy & Commerce committee with this crucial endeavor.

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Recommendations

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Thank you for the opportunity to share APA's recommendations to ameliorate regulatory barriers to medical innovations and support the federal investments necessary to identify and utilize 21st century cures. APA is happy to be a resource for psychiatric research expertise and we look forward to working with you as the Committee's investigation continues.

Sincerely,

Paul Summergrad, M.D.
President

Saul Levin, M.D., M.P.A.
CEO and Medical Director

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June 10, 2014

Energy & Commerce Committee

Re: 21st Century Cures Input

Dear Chairman Upton and Representative Degette,

Thank you for the opportunity to comment on the "21st Century Cures" initiative. We applaud your efforts and believe that it is important to address the challenges in drug and device discovery and development.

Attached please find our comments.

Sincerely,

[redacted]

Allan Coukell
The Pew Charitable Trusts

Spurring Antibiotic Innovation

Thank you for the opportunity to submit comments to the 21st Century Cures initiative. These comments are being submitted by the Antibiotics and Innovation group at the Pew Charitable Trusts. Pew is an independent, nonpartisan research and policy organization that has made a multi-year commitment to advancing public policies to spur the development of new antibacterial drugs. As the Committee considers the challenges to medical product discovery and development, we urge that one focus be the obstacles to developing new antibiotic drugs because of the public health importance of these critical therapies.

Antibiotics are one of the greatest success stories in modern medicine. Without them, women would be more likely to die in childbirth, surgeries would be more dangerous, and cancer treatments would expose patients to untreatable infections. Evolving resistance continually chips away at our antibiotic supply, making a robust pipeline essential. However, because antibiotic infections are opportunistic and often secondary to another illness, there is no cohesive patient advocacy coalition calling for better cross-sector cooperation or pushing for antibiotic drug discovery. There will be no organized marches on Capitol Hill seeking to compel members of Congress to make antibiotic drug discovery a national priority, so it is important that Congress recognize and address this urgent public health need.

The history of antibiotics is a race between innovation and resistance – as innovative science furnishes novel drugs, bacterial evolution can quickly render them ineffective. And, in fact, the problem of antibiotic resistance is real and growing. Drug-resistant bacteria are spreading in our hospitals and our communities. According to a 2013 report by the Centers for Disease Control and Prevention (CDC), more than 2 million people a year are sickened by drug-resistant infections, and more than 23,000 die as a result.[i] In the past few years, pathogens resistant to multiple antibiotics, so-called "superbugs", have emerged as an even greater public health concern. Doctors already face patients with untreatable infections, and threats such as carbapenem-resistant Enterobacteriaceae (CRE) – which CDC calls a "nightmare bacteria" – hint at the potential of worse to come. CRE has spread rapidly across the nation, from one medical facility in one state in 2001 to medical facilities in 47 states and counting as of February 2014.[ii] Nearly half of hospital patients who contract bloodstream infections from CRE will die from this infection.

The pipeline of new antibiotics is running dry. The World Health Organization recently concluded that we may be entering the very real possibility of a "post-antibiotic" era in the 21st century. Drug makers developed 13 new classes of antibiotics between 1935 and 1968, but only three new classes since that time. Pew analysis found 45 new antibiotics currently in clinical development. However, on average, only one in five to one in ten drugs that make it to the initial phase of clinical trials receive Food and Drug Administration (FDA) approval. Given this failure rate, it is clear that there are too few drugs in development to meet current and anticipated patient needs.

Three principal challenges present obstacles to antibiotic drug development:

- The first is economic: Antibiotic drug development is a poor return on investment compared to "blockbuster" drugs such as those for high blood pressure or cholesterol.

- The second hurdle is regulatory: Existing approval pathways are not well tailored to meeting our most pressing needs for new antibiotics – those to treat serious or life threatening infections for which few or no treatment options currently exist.

- The third challenge is scientific: Fundamental scientific challenges and a need for a more robust clinical trial insfrastructure hinder the development of new antibiotic drugs.

Economic Solutions

Members of Congress have taken the threat of antibiotic resistance seriously. In 2012, Congress passed the Generating Antibiotic Incentives Now (GAIN) Act, as part of the Food and Drug Administration Safety and Innovation Act. This bipartisan legislation extends by five years the exclusivity period during which antibiotics that treat serious or life-threatening infections can be sold without generic competition. This increases the potential for profits from new antibiotics by giving innovative companies more time to recoup their investment costs. As of June 2014, at least 18 novel antibiotics in development have been designated as qualified infectious disease products (QIDP) under GAIN and one product has reached market. While the GAIN incentives are an important first step, the antibiotic pipeline is not nearly robust enough and more work is needed.

Regulatory Solutions

Regulatory approval for drugs to treat highly resistant bacterial infections is especially challenging because only a small number of patients contract such infections and meet the requirements to participate in traditional clinical trials. These are daunting odds for any company, but especially challenging for small companies.

In order to address some of the regulatory barriers to antibiotic development, Representatives Phil Gingrey and Gene Green have introduced the bipartisan Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742. This legislation would help streamline the regulatory pathway for antibiotics that could address CRE and other dangerous pathogens. It directs the FDA to approve new antibiotics for specific, limited populations of patients with life-threatening infections where few or no treatment options currently exist.

This pathway was endorsed by the President's Council of Advisors on Science and Technology in its 2012 report. While the PCAST recommendation was broader than antibiotics, the report specifically called out antibiotics as appropriate for this pathway. Specifically, PCAST said:

> Currently, FDA may not grant approval without extensive clinical trials in the larger population due to concerns about safety risks resulting from possible off-label use in broader groups. It would be desirable to have a pathway under which such drugs could rapidly reach high-need patients while reducing the risks from wider use of the drug. In the case of antibiotics, there would also be clear public health benefits to limiting the use of new antibiotics effective against drug-resistant bacteria, to stave off the emergence of drug-resistant strains.

ADAPT would implement this recommendation by directing the FDA to create this pathway, allowing FDA to approve antibiotics for use in limited populations.

PCAST recommended that the approval pathway be accompanied by a designation that would "send a clear and effective signal to patient, physicians, payors and malpractice insurers that the drug should be reserved for use in the specific subgroup of patients. The …designation would not forbid off-label use, but would be intended to affect the likely usage by shifting responsibility to educated prescribers and payors. In doing so, it would shift the overall benefit-risk balance and allow the FDA to responsibly approve drugs intended for patients with the serious manifestation."

As PCAST points out, the intent of the designation is not to prohibit off-label use, and the ADAPT legislation appropriately includes language that makes it clear that this legislation would not limit the practice of medicine. While ADAPT does have a labeling provision, the language should be strengthened in order to fully achieve the goals laid out by PCAST. Specifically, antibiotics approved under this pathway should be clearly labeled with a visual element or other branding so that prescribers and dispensers can immediately know that the risk/benefit calculation FDA made in approving the LPAD drugs was specific to the patient with no other options and that the drug may not be appropriate for patients who have other treatment options.

Pew, the Infectious Diseases Society of America, and a number of other prominent provider and public health groups are advocating that ADAPT be amended to allow for this kind of designation so that the legislation will fully implement the intent of the pathway. With this one alteration, ADAPT would help to fill an urgent public health need by providing a pathway for the most essential new antibiotics to reach the patients who need them.

Because the threat of antibiotic resistance is pressing and increasing, we urge the committee to consider moving ADAPT as an immediate first step in this important new initiative.

Scientific Solutions

Addressing the economic and regulatory barriers to antibiotic drug development are critical steps, but ensuring that new therapies continue to become available will also require attention to

the basic science that primes the antibiotic drug pipeline. Without innovative antibiotic research, we cannot hope to stay ahead of drug resistance.

Current research is not addressing fundamental scientific questions that are long-standing obstacles to antibiotic drug discovery. For example, we do not fully understand how to get drugs into, and prevent them from being expelled from, the formidable Gram-negative bacteria that include many of the most dangerous pathogens.

NIH has begun to address the gap between basic research and commercial products through unprecedented federal funding for translational science. While this work is critical for addressing antibiotic resistance, it is not enough.

In order to best leverage public and private investment, we need new, creative partnerships to tackle fundamental scientific problems that slow antibiotic discovery and development. Other countries have already begun to foster better communication and collaboration between academia and industry – the Innovative Medicines Initiative (IMI), for example, is a partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations that supports research and development projects between industry and academic researchers. The PCAST 2012 report recommended the creation of a similar broad-based partnership to promote innovation and improvement in the discovery, development, and evaluation of new medicines for important public health needs.

Federal investments can also make clinical trials more feasible, bringing down the costs of drug development and potentially speeding up development time. Clinical trials for antibiotics pose particular challenges for both enrollment and outcomes assessment: the need to start treatment urgently complicates trial enrollment, and treatment often begins prior to the availability of culture and sensitivity results, posing challenges for subject selection. A clinical trials network that could be used by industry as well as academics would facilitate drug development, particularly for small companies.

Antibiotic resistance is a societal issue that requires partnership and collaboration across government agencies, including NIH, CDC, and FDA, and between academia and industry partners. We are depending on leaders in Congress to help ensure that federally funded antibiotic research is coordinated and supports promising ideas and innovation by tackling long-standing obstacles to antibiotic drug discovery and exploring new areas of science to develop innovative approaches to address growing antibiotic resistance.

Conclusion

Antibiotics not only treat acute infections, but also underpin much of health care – interventions ranging from routine surgical procedures to organ transplants and cancer treatment rely on the availability of effective antibiotics. As the Committee considers how to move medical innovation forward, the availability of effective antibiotics will be important to ensuring the viability of a wide range of other therapies. By moving the ADAPT Act in the near term, and

focusing long-term attention on research and clinical trials, the 21st Century Cures initiative could have a lasting impact on the antibiotic drug pipeline, and help ensure the continued availability of the wide range of medical treatments that are only possible because of the availability of the antibiotics they depend on.

* * *

Big data can accelerate patient access to new medical products

The following comments are submitted on behalf of the Medical Device group at the Pew Charitable Trusts. The device project works to foster innovation that will benefit patients and to improve medical device safety, in particular through improved postmarket surveillance.

As Congress considers the challenges to medical product innovation, it will be important to consider whether there are ways to facilitate the clinical trials that are so important to get the data about whether a product is safe and effective. This data is critical to regulators, payers, clinicians and patients so they can make informed decisions. The development of new drugs and medical devices for patients can take more than a decade and cost more than a billion dollars. The clinical trials needed to obtain data to assess the safety and effectiveness of new products are the primary contributor to the length and cost of product development. The answer to this conundrum is not to do away with this vital scientific tool, but rather to develop more efficient methods and trial infrastructure.

The expansion of health information technology and increased adoption of electronic health records (EHRs) have the potential to dramatically decrease the costs and time of products to market without sacrificing data on safety and effectiveness. These new tools can aggregate large amounts of information—known as big data—to support drug and medical device innovation.

A recent clinical trial conducted in Europe demonstrated the ability of these electronic tools to quickly collect large amounts of data without breaking the bank. Researchers used established registries—databases that contain information on patient outcomes—to evaluate whether a specific procedure helped patients with heart attacks. By using these data, they conducted a "registry-based randomized clinical trial" involving more than 7,000 patients that lost no one during the follow-up period. This unprecedented study only cost $300,000, roughly $50 per patient. Conducting such a study outside of a registry in the United States would cost hundreds of millions of dollars, if not more. The study—known as the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial—demonstrates the value of registries to efficiently—and cost-effectively—conduct large clinical studies.

What are registries?

Put simply, registries are large databases that collect information on a group of patients treated for a particular medical condition so that their outcomes can be assessed over time. Medical product registries focus on patients who have used a certain drug or medical device in order to understand how well it has worked.

Typically, medical product registries in the United States have been used to conduct postmarketing surveillance by tracking the experience of a broader patient population for a longer period of time than was studied in premarket clinical trials. Hip implants, for example, are expected to last 15-20 years but typically require only two years of clinical data for FDA

approval. Registries can be a cost-effective way to study devices such as these for longer periods of time.

An example of a high-performing registry is the Australian Orthopaedic Association National Joint Replacement Registry, which was implemented in 2002 to improve quality of care for patients receiving implanted prosthetics. In 2007, the registry showed that metal-on-metal hips—introduced in 2003 for younger patients needing hip replacements—failed at a rate more than two times higher than conventional hips, leading to a worldwide recall of the problematic hips.

The United States also has large registries, such as the American College of Cardiology's National Cardiovascular Data Registry which collects data to improve the quality of cardiovascular care through a suite of hospital-based and outpatient registries. FDA has used data from this registry to investigate potential safety problems with cardiac devices. This registry, though, does not routinely conduct analyses on medical products.

Registries have the potential to become a pillar of the data collection infrastructure in the United States and to provide patients, clinicians, payers, manufacturers and regulators with information on the safety and effectiveness of products used in care.

Registries' role in expediting patient access to new products

Registries can also play a critical part in efforts to accelerate patient access to new products by efficiently collecting robust information on safety and effectiveness. They can promote innovation in a number of ways.

First, registries can serve as platforms for more efficient premarket clinical trials. As demonstrated by the TASTE trial, registries can collect data on outcomes from thousands of patients at low cost over extended periods of time. In another example, FDA approved an expanded indication for an innovative heart valve based on the use of an existing registry.

Dr. Jeff Shuren, director of FDA's Center for Devices and Radiological Health, mentioned this example at the Energy and Commerce Committee's roundtable last month. He stated, "We very recently actually allowed for expansion of the labeling indication on the device, where the company and two health care professionals societies were going to do a clinical trial and we told them don't do it, don't waste your time. We looked at the registry data and we said we think it is good enough."

Robust postmarket data on patient outcomes can also provide manufacturers with more information to inform the next generation of product development. Registries can efficiently collect data on large numbers of patients, making it easier understand how the product works in various patient subpopulations. As health care embraces personalized medicine, discerning differences in how patient subgroups respond to treatments will become increasingly essential to the next generation of cures.

With this information, manufacturers can refine their product or update labeling to address concerns raised by the data, develop new tests to better identify patients for whom the product would work best, and utilize the data to develop new products for patient subpopulations. This infrastructure creates a feedback loop to continuously inform product development and accelerate treatments for patients in need.

Finally, sophisticated tools—like registries—to collect robust postmarket data on patient outcomes can support recent efforts by Congress and FDA to speed access to drugs and devices. FDA may be reluctant to approve products more quickly if the agency is not confident that safety problems will be detected in the postmarket setting. To mitigate risks, FDA must have strong postmarket data collection tools, such as registries, to collect needed data on the safety and effectiveness of the products.

Challenges to registry adoption

Despite the proven value of registries to facilitate innovation, there are a number of challenges that must be overcome to enhance their adoption.

First, despite the dramatic uptake of EHRs and other electronic health information sources, these systems cannot easily transmit data among one another. This lack of interoperability, for example, prevents data transmission across EHR systems developed by different manufacturers.

It also hinders the ability for registries to extract clinical and outcomes data from EHRs. Instead, registries must develop the ability to extract information from the EHR systems at each facility, or require manual entry from providers. The Office of the National Coordinator for Health Information Technology (ONC), under the leadership of Dr. Karen DeSalvo, has made interoperability a top priority. ONC last week released a policy paper outlining its 10-year vision for health information technology interoperability, including both short- and long-term goals. We urge the Committee to lend its full support to interoperability efforts.

There are also potential advances in clarifying when registries must obtain patient consent, and what level of federal privacy protections apply. There are two policies that regulate patient consent and privacy protections: (1) the Common Rule, which requires that human research participants give fully informed consent, and (2) the Health Insurance Portability and Accountability Act (HIPAA), which provides federal protections for individually identifiable health information and security standards for transmitting health information. The differing—and sometimes conflicting—requirements in the Common Rule and HIPAA create a barrier for collecting patient data for registries. Registries have sought clarity on the level of patient consent that is needed, given their use of data that is collected as part of usual clinical care.

While individual privacy is of paramount importance, but progress in healthcare and medical product innovation depends on improving our ability to collect and use aggregate data efficiently and effectively. Identifying the appropriate balance requires additional conversations among stakeholders, including Congress.

The Pew Charitable Trusts—in conjunction with the Blue Cross and Blue Shield Association and the Medical Device Epidemiology Network Infrastructure Center at Weill Cornell Medical College—convened a series of meetings with stakeholders to begin addressing some of the issues facing registries. We will release a report based on our findings within the next few weeks.

Conclusion

Given the proven value of electronic health information and registries – and the much greater potential yet to be realized, Congress should explore whether statutory changes are required to maximize the potential of these data sources to expedite patient access to safe and effective medical products. Tthrough its oversight capabilities, Congress can also ensure that the Administration is aggressively supporting efforts to harness the power of big data to improve the lives of patients.

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[i] Centers for Disease Control and Prevention, Antibiotic Resistance Threats to the United States, 2013, http://www.cdc.gov/drugresistance/threat-report-2013/index.html.

[ii] "Tracking CRE", Centers for Disease Control and Prevention, last modified February 10, 2014. http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html.

United for Medical Research

June 9, 2014

Chairman Fred Upton
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Representative Diana DeGette
House Energy and Commerce Committee
2368 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Upton and Representative DeGette:

United for Medical Research (UMR) represents leading research institutions, patient and health advocates and private industry, joined together to seek steady increases in federal funding for the National Institutes of Health (NIH) in order to advance the development of new and better treatments. We appreciate the work the Committee is doing through the 21st Century Cures Initiative and would like to express our strong support for continuing our nation's commitment to biomedical research, so that we may remain the world leader in the life sciences. Below please find UMR's response to the white paper entitled "21st Century Cures: A Call to Action".

NIH is an economic driver and jobs creator, an irreplaceable source of federal investments in basic research, and most importantly, the foundation for extraordinary improvements in our health, longevity, and quality of life. Further, NIH funding is often the catalyst for the private investment that ultimately leads to new treatments for patients.

NIH Research is Critical to Private Sector Innovation

A steady stream of medical advances, from new drugs and devices to improved diagnostics and cutting edge technologies, are the byproduct of federally funded research discoveries. The biomedical research pipeline is a partnership between the 325,000 scientists funded by NIH, performing research at 3,000 institutions in all fifty states and the private sector. Private industry provides the products to support research discovery and brings research breakthroughs to fruition and into the marketplace. It also develops the discoveries that are the result of NIH-funded research, turning them into diagnostic tools and treatments that help avoid needless suffering and save countless lives.

As Senator Richard Durbin recently asserted, "In the last two centuries, U.S. government support for scientific research has helped split the atom, defeat polio, conquer space, create the internet, map the human genome, and much more. No nation has ever made such a significant investment in science, and no nation's scientists have ever done more to improve the quality of life on Earth."

NIH supports the highest-quality science and trains the next generation of medical researchers, ensuring that the pipeline of knowledge and talent does not run dry. The private sector's ability to maintain the rate of medical advancements depends in large part on a sustained commitment to NIH. One of the biggest obstacles to scientific progress has been a decade of budgets that have failed to keep pace with biomedical inflation and a $1.6 billion cut due to sequestration. NIH's loss of purchasing power over the past decade is alarming. NIH Director Dr. Francis Collins recently underscored this point when he said, "NIH is the largest supporter of biomedical research in the world, but we are losing our edge. Since 2003, we've seen a steady decline in support, down to about 25 percent below where we were 10 years ago in terms of our power to fund research."

NIH as an Economic Engine

"Growing and sustaining a viable, long-term innovation eco-system is the smart choice and the only choice that makes sense for patients and for our national economy," noted John Castellani, President and CEO of PhRMA. NIH-supported research triggers private investment and significantly contributes to job growth and the overall strength of the U.S. in the global health care market.

As Congressman Jack Kingston (R-GA), Chair of the Labor/Health and Human Services/Education and Related Agencies testified at a recent hearing, "NIH's support for extramural basic research provides the 'seed corn' for the private sector to create new, innovative preventable digital medicine."

A 2012 report by UMR entitled *"NIH's Role in Sustaining The U.S. Economy"* shows that NIH has as vital role in fueling economic growth in the health and life sciences industry. However, it also showed that the lack of sustained investment in the agency is beginning to have an impact. The decrease in NIH funding between 2010 and 2011, which was in part attributable to the end of supplementary funding by the American Recovery and Reinvestment Act, forecasted a decrease of approximately 55,000 jobs nationwide. This coupled with the $1.6 billion cut in funding due to sequestration has had real and lasting effect on jobs and research.

As the data clearly show, there is an urgent need to re-prioritize our support for biomedical research and this critical job sector by providing NIH with increased funding to counteract the effects of a budget that for the last decade has not kept pace with inflation and blunt the catastrophic impact of sequestration.

NIH Provides Hopes to Millions

Although its importance to the nation's economy is remarkable, we must not forget NIH's primary mission: to improve the health of the nation. NIH has been tremendously successful in improving human health and its accomplishments are numerous and well documented: a nearly 70-percent reduction in the death rate for coronary heart disease and stroke; advances in HIV/AIDS treatment that put an AIDS-free generation within reach; nearly one million lives saved due to decreases in cancer death rates over the past decade; and steady increases in life expectancy.

Moreover, as our understanding of the human genome grows at an exponential rate, we have entered an era of personalized medicine where intervention on an individualized level is beginning to generate story after story of children and adults whose lives have been saved through cutting-edge research advances. These human stories of triumph over disease and scientific opportunity serve to provide hope to millions of patients whose diseases and conditions are still waiting for the next generation of treatment or cure.

Looming Threats: Global Competition and Sequestration

"Investing in research has huge paybacks, paybacks in improving the human condition and paybacks in reducing health costs as you get new tools," noted Bill Gates, Microsoft founder and Co-Chair of the Bill and Melinda Gates Foundation, when he visited NIH last year. Indeed, Congress' wisdom in investing federal dollars in NIH has yielded phenomenal dividends and made the U.S. the undisputed world leader in life science innovation.

However, ever-shrinking budgets have made it difficult to maintain that leadership. Other nations are following in our footsteps to fuel their own biomedical research enterprises, even as we take a step back. China, India, the European Union, and Russia have all declared their intentions to increase their research investment, despite the fiscal challenges presented by the global economy.

"From 2007 to 2012, countries average annual investment in biomedical R&D increased 33 percent in China, 12 percent in South Korea, 10 percent in Singapore and it fell by two percent in the United States," Congresswoman Rosa DeLauro, Ranking Member of the Labor/Health and Human Services/Education and Related Agencies Appropriations Subcommittee recently said. Losing our competitive edge in biomedical research is a clear and present danger to the crucial economic contributions of our life sciences innovation ecosystem.

Research Only Supported by NIH

The history of NIH research in the molecular discoveries that are the basis for countless vaccines, diagnostics, and treatments is well-established. What is somewhat less appreciated is the equally important and broader scientific portfolio that has a proven track record of saving and improving lives of the American public.

Prevention is a central strategy for every chronic disease in the in the United States. Research supported by the NIH has led to the development of what are now well-established, evidence-based preventive options for heart disease, diabetes, certain types of cancer, and many other diseases. Diseases that lack prevention strategies not only require better treatments, they need research that will produce a way of preventing them, as well. Such progress would not only save countless lives, it would ease the burden on our health care system and result in significant economic savings as well.

When people do get sick, it is important not to just treat the disease but to treat the patient as well. NIH supports research that improves how patients are treated when receiving a curative treatment. This research strives to reduce the toxicity and side effects of treatments, better manage symptoms, and ensure the needs of patients are being met. One example of how this is done is

through clinical trials that study existing therapies to determine whether a lower dosage or shorter treatment regimen would result in the same curative outcome as a higher dose or longer regimen, but with fewer significant or long-term side-effects. For people living longer with heart disease, cancer, and other chronic conditions, the impact on a person's quality of life and productivity cannot be overstated.

Research like this does not happen without NIH support and it is an integral part of NIH's research portfolio. It also has a significant impact and benefit on the U.S. economy and the well-being of our fellow citizens.

NIH Should Remain a U.S. Priority

John Lechleiter, the CEO and chairman Eli Lilly & Co., once stated, "There's no better investment that we can make than in biomedical research and in our health. This is not something that we're trying to steal away from someone else... America leads the world."

We could not agree more. Increased investments in biosciences through the only federal agency specifically designed for this purpose —NIH — makes more sense than ever.

For our economy, for our position as a world leader, for the health of our citizens, UMR respectfully requests that as you move forward with the 21st Century Cures Initiative and include a strategy for providing the NIH with a path toward stable, sustainable and predictable growth.

Sincerely,

Members of United for Medical Research

Mauro Ferrari, Ph.D.
President and CEO
Houston Methodist Research Institute
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The Honorable Fred Upton
21st Century Cures Initiative
House Energy and Commerce Committee
2125 Rayburn HOB
Washington, DC 20515

The Honorable Diana DeGette
21st Century Cures Initiative
House Energy and Commerce Committee
2322A Rayburn HOB
Washington, DC 20515

Dear Chairman Upton and Representative DeGette:

On behalf of Houston Methodist and the Houston Methodist Research Institute (HMRI), we thank you for establishing the 21st Century Cures Initiative. Your bold examination of the challenges presently facing our nation's global stature in the field of medicine is well-needed and we hope to add to your conversation. Innovation in medical research is more prolific than ever before, but roadblocks exist in the process that hinder the progress of potential treatments and technologies.

In contrast, at Houston Methodist we have seen great success in our "bench to bedside" translational research model that integrates cross-disciplinary research teams consisting of Houston Methodist doctors and HMRI scientists and experts. Our translational research is based on the most important goal: efficiently and effectively finding cures and technologies that improve and save lives, and getting them to patients as quickly and safely as possible.

By working within one vertical hospital-based system, Houston Methodist is able to achieve a seamless transition between basic research discoveries and translational research results. In combination with our partnerships with institutions of higher learning, our cutting edge facilities provide an efficient and effective strategy for overcoming common medical research hurdles and expediting the development of innovative therapies and treatments with demonstrable results.

Bridging the Valley of Death

At many institutions, innovations that could address some of the worst health afflictions, such as cancer, heart disease and Alzheimer's, are abandoned due to a lack of funding and lack of integrative expertise and capabilities. The major hurdles that most medical research discoveries never overcome comprise what many researchers have come to call the "Valley of Death" (Figure).

Often, institutions are unable to bridge research discoveries and preclinical trials with FDA-approved clinical trials because of a lack of comprehensive medical research facilities and research expertise. Parts of their research have to be repeated by a second institution to fulfill FDA requirements, resulting in additional time and expenses. However, hospital-based research teams with access to specialized research facilities and advanced medical technology like HMRI are uniquely positioned for success in guiding medical innovations through the process in a cost effective and time efficient manner.

HMRI is physically connected to the Houston Methodist hospital, which encourages and facilitates a culture of innovation. Multidisciplinary teams of doctors, scientists and subject matter experts are easily able to collaborate on streamlined "bench to bedside" translational research projects. Our research facilities are at the forefront of technology and include two Good Manufacturing Process (GMP) facilities which are necessary to manufacture small amounts of experimental clinical-grade materials for research. We are also home to the only academically-owned and operated cyclotron in the State of Texas, which enables us to create radiopharmaceuticals for research and medical applications.

Forward-thinking translational research institutions like HMRI house the expertise, facilities and collaborative multidisciplinary partnerships to overcome common impediments. However, a universal challenge to all research institutions is a shortage of funding. Phase I clinical trials and Phase II clinical trials are extremely costly, and without subsequent funding for Technology Readiness Levels (TRL) 4, 5, and 6, even the most effective new medical research treatments and technology cannot be handed off to industry partners that can produce them on a large scale. What governmental agencies define as research and development within the field of maturing technologies does not cover the full process, leaving researchers without certainty of funding

By funding translational research, patient knowledge can be turned into innovative cures and treatments that will make real and lasting differences in the lives of those that have funded it through tax dollars.

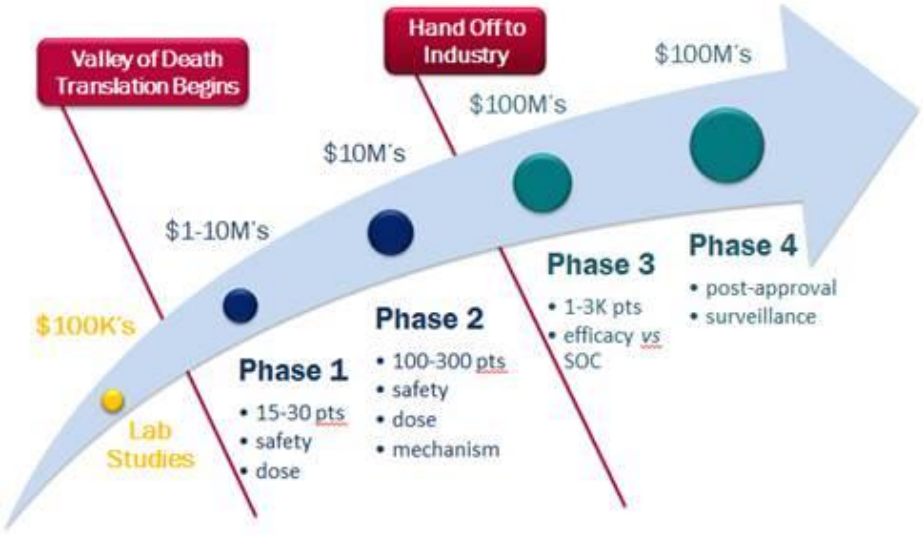

Figure. Forward-thinking institutions dedicated to translational research like Houston Methodist Research Institute have the research expertise, integrated multidisciplinary collaborative partnerships and specialized research facilities needed to seamlessly transition between phases in the research continuum and guide medical innovations through the process in a cost effective and time efficient manner.

Houston Methodist Research Institute

Houston Methodist Research Institute focuses on research programs that go beyond basic science and theoretical research to focus on innovative patient-centered research that offers new treatments and technologies. Houston Methodist Research Institute's "bench to bedside" translational research approach is reflected in our history of medical innovation and the research happening today.

Houston Methodist orthopedic surgeon Dr. Brad Weiner is working to do more for his patients facing amputations due to bone injuries that cannot be healed or repaired without major invasive surgery involving bone grafts, plates and screws that can take months to heal. He is now collaborating with nanomedicine researcher Dr. Ennio Tasciotti at Houston Methodist on a new nanomaterial he developed to heal and regenerate bone tissue, faster and stronger than the normal healing process. The original material was created with collaborators from Harvard, UTHealth, MIT, Texas A&M University and Northwestern University. Their medical solution is called "bone putty."

The duo collaborated with the University of Akron and Texas A&M University, and sought guidance from industry partners Akron Polymer Systems, Finceramica, and Lubrizol to figure out how to manufacture prototype materials and further develop the approach. Together, they were able to heal sheep with traumatic bone injuries that would normally require amputation. With the putty, amputation was avoided and the sheep was able to run and walk naturally in a matter of weeks.

The applications of bone putty to medicine are substantial. When an individual suffers major damage to bone tissue, they are left with the difficult choice of major limb amputations or bone reconstruction through rods, pins, plates and other devices. Often those foreign objects must be removed or realigned in additional invasive surgical procedures. There are many instances of more than a dozen surgeries to preserve the limb. A better choice for the patient, their family, and their doctor is the prospect of using bone putty to rebuild the bone more quickly while preserving the ability of the individual to bear weight on that limb.

The multi-institutional team at Houston Methodist has access to the expertise and facilities they need for the next stages of clinical trials. Through a grant from the Department of Defense and philanthropic institutions, we were able to do the initial GLP FDA-approved studies. Now HMRI is eagerly working to complete our testing on large animals so we can transition to human trials. The goal of the team and the funding agencies is to make bone putty available for traumatic injuries in military personnel, but it has equally tangible and usable civilian applications.

The entire protocol is written and ready for FDA submission once the remainder of the testing is completed. They are actively seeking funding to advance to Phase I clinical trials. With further funding, bone putty can be ready for patient clinical trials within one to two years. Private industry has also expressed interest in the products when they reach this stage for development and delivery to patients.

The team hopes that after approval for the purpose of healing military personnel with traumatic injuries, bone putty will then be quickly approved for other applications like slow-to-heal injuries in children and older adults, as well as bone conditions such as rheumatoid arthritis and osteoporosis.

Congressional Efforts to Reform the Process

Establishing the 21st Century Cures Initiative is one of the most necessary and pragmatic steps Congress has taken on improving the success of medical research. We believe your efforts will uncover scores of realistic solutions that can expedite the delivery of innovative medical technologies. We would like to offer two.

First, government participants in the 21st Century Cures should undertake a serious dialogue with industry about the viability of maturing technologies. What government and what industry consider "research" and "development" are not aligned. The result is the aforementioned "Valley of Death" that occurs in the validation of products. It has created a medical no-man's land in which trailblazing advances wither on the vine at the very time they should be encouraged further.

Other complications for researchers and innovators arise from jurisdictional limitations within Congress and between executive agencies. The Committees on Energy and Commerce, Science, Space and Technology, Armed Services, and Veterans' Affairs all have jurisdiction over various agencies and their respective biomedical research programs. A similar problem occurs in the Senate as well. The result is that each agency has compartmentalized statutes, regulations, and guidelines that make it difficult for medical researchers to concurrently work with multiple agencies. This lack of cohesion delays and increases the costs of bringing technologies to clinical practice.

By creating synchronized biomedical research policy across jurisdictional lines at the congressional and agency level, scientists will be able to satisfy requirements and achieve benchmarks more efficiently. The challenges we face in this matter are systemic, so we suggest Congress approach this issue from a government-wide approach rather than focusing on any specific agency.

A Vision for the Future

By committing to the vision of translational research, Houston Methodist has seen great success in our "bench to bedside" translational research model. Further, it integrates cross-disciplinary research teams consisting of Houston Methodist doctors and Houston Methodist Research Institute scientists and experts to turn our wealth of talent and medical knowledge into real solutions that help people live healthier lives.

We invite you to visit the Houston Methodist Research Institute, located in the world-renowned Texas Medical Center, to see first-hand how our state of the art medical technology and team-based, doctor-driven and patient-focused translational research approach is turning basic research into the innovative medical breakthroughs the public needs.

Thank you again for your support of successful and innovative medical research through the 21st Century Cures Initiative. Please do not hesitate to contact me if I can be of assistance in answering any questions on HMRI or translational research.

Sincerely,

Mauro Ferrari, Ph.D.
President and CEO
Houston Methodist Research Institute
Executive Vice President
Houston Methodist

June 10, 2014

The Honorable Fred Upton
Chairman
The Honorable Diana DeGette
Member
Committee on Energy and Commerce
United States House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515
cures@mail.house.gov

Dear Chairman Upton and Representative DeGette,

21st Century Cures: Quintiles Comments

This letter is in response to your bipartisan 21st Century Cures initiative. Quintiles (NYSE: Q) fully supports the initiative and its goals of saving more lives and keeping the United States as the leader in medical innovation. We welcome the opportunity to comment on possible approaches to closing the gaps between advances in scientific knowledge and the regulatory policies needed to accelerate the delivery of innovative therapies to patients.

Quintiles is the world's largest provider of biopharmaceutical development and commercial outsourcing services with a network of more than 29,000 employees conducting business in approximately 100 countries. We offer a unique vantage point across companies, therapeutic areas, geographies, and product types. Over the past six years, Quintiles has worked on clinical trials involving nearly 8.5 million patients worldwide. The company has helped to develop or commercialize today's top 50 best-selling drugs and top 20 best selling biologics. We have been involved with over 100,000 successful trial designs and 110 product launches. We have experience in 1,000+ early clinical studies (Phase I/IIa) and are the most experienced Phase II/III provider. We also have experience of over 400 observational studies and patient registries.

Your white paper, 'A Path to 21st Century Cures' (May 1, 2014), lays out many key issues and poses provocative questions. Our response focuses on the following four areas:

1. **Alternative Development Pathways** to speed the introduction of new therapies that would address unmet medical needs for patients with serious or life-threatening conditions as alternatives to the traditional three-phase clinical trial paradigm.

2. **Master Protocols and Adaptive Designs** to improve the productivity of drug development, reducing failure rates, lowering costs, reducing duplicative research, and accelerating availability of better drugs.

3. **Standardizing and Harmonizing** requirements for data and documentation, to reduce paperwork, clinical trial timelines, and complexity.

4. **Improving Data Collection and Accessibility to Accelerate the Transition from 'Analog to Digital' Drug Development**, with public and private entities alike enabling the evolution of clinical trial design and conduct from the traditional "analog and local" model to a "digital and global" one. This includes continued investment in technologies and tools.

These four areas are addressed below:

1. Alternative Development Pathways

The Challenge

It currently takes an average of over seven years of total development time for New Molecular Entities,[1] including large, expensive Phase III studies required to demonstrate safety and efficacy in a broad population. This does not include the consideration that the risk/benefit relationship can differ sharply depending on the severity of the patient's illness and the availability of alternative therapies. Therapies that could benefit smaller subsets of populations take longer to develop in today's model and face the prospect of not reaching those specific patients because of the 'up or down' determination of safety and efficacy for the broader population.

The creation of the Breakthrough Therapy designation and other expedited drug *approval* pathways is a welcome advancement, and we applaud the effort, including use of surrogate endpoints, early consultation for more efficient trial design, the increasing use of biomarkers, etc. However, the actual time savings offered focuses on FDA review time (reducing from average of 10 months to six) versus providing a condensed *development* timeline, which currently ranges from 5-10 years to advance through the three-phase model.

A Solution

Quintiles strongly supports the adoption of alternative development pathways to speed the introduction of new therapies that would address unmet medical needs for patients with serious or life-threatening conditions. An example of this is the Adaptive Licensing approach that the European Medicines Agency (EMA) is now piloting.[2] In 2013, a similar alternative pathway approach was the subject of an FDA public hearing.[3] Under the FDA proposal, "the drug's safety and effectiveness would be studied in a smaller subpopulation of patients with more serious manifestations of a condition. Such a pathway could involve smaller, and more focused clinical trials than would occur if the drug were studied in a broader group of patients with a wide range of clinical manifestations. The use of biologically and clinically meaningful surrogates as non-mortality endpoints should be allowed. The labeling of drugs approved using this pathway would make clear that the drug is narrowly indicated for use in limited, well-defined subpopulations in which the drug's benefits have been shown to outweigh its risks." Allowance of such designs and endpoints should obligate Sponsors to conduct evaluations of longer-term, post-approval safety and outcomes.

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[1] http://csdd.tufts.edu/files/uploads/Outlook-2013.pdf

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

[3] https://www.federalregister.gov/articles/2013/01/15/2013-00607/creating-an-alternative-approval-pathway-for-certain-drugs-intended-to-address-unmet-medical-need

Quintiles' research suggests that patients are willing to use therapies developed under an accelerated pathway. This is based in part on a 2012 survey of patients living with chronic disease, which found that patients want access to new medicines sooner, and that those in greatest need are willing to accept more uncertainty about a new therapy if it offers potential to improve their health:[4] 71% of U.S. patients surveyed agreed that: "*We take too long to make drugs available, which costs lives by forcing people to go without potential beneficial therapies*.

Quintiles maintains not only that such a pathway is an important way to bring new therapies to patients in need, but also that it is a feasible pathway that can be operationalized today.

Recommended Approach

FDA should adopt, on a pilot basis for conditions meeting agreed criteria, an alternative development pathway where new entities meeting safety and efficacy endpoints (including clinically and biologically meaningful, non-mortality surrogates) in smaller, well-defined populations are granted limited market approval for that specific sub-population. The sponsor would then conduct additional studies on expanded populations to evaluate safety and potential expansion of label to broader population, while monitoring real-world outcomes in treated patients.

Today's technologies and science provide the ability to keep patients safe while accelerating access in ways not envisioned with the original Gold Standard three-phase randomized clinical trial (RCT) model. Below are five key capabilities to operationalize this approach. Each would improve drug development today. Together they would allow for the more aggressive step of allowing an Alternative Development Pathway. They would create a rigorous, confidence-inspiring pathway based on pre-registration studies in narrowly defined subpopulations, together with post-marketing registries and observational studies to ensure safe use:

a) **Data Analytics to Power Accurate Studies***:* The first key to making this work is being able to incorporate real-world data to inform trials. Quintiles and others have this capability and use it today. Congress should: 1) direct FDA to encourage its use; and 2) drive availability of de-identified data. This would enable better planning and design of pre-registration trials in stratified subpopulations so that these studies have the maximum likelihood of providing clinically and statistically significant findings. Advanced trial design tools are available now to incorporate real-world data into trial designs. For example, we use a tool called Quintiles Infosario™ Design that allows us to interrogate real-world data including de-identified electronic medical records (EMRs) representing more than eight million patient lives. With this capability, questions such as "What are the anticipated event rates for specific sub-populations?" and "What sites are likely to see the specific populations eligible for this treatment?" can be answered. Those insights then can be used to perform simulations of possible trial designs in real time to yield more informative and efficient studies.

b) **Precise identification of the patient subpopulation**. Recent advances allow for the use of genomics, RNA sequencing, expression analysis, soluble and tissue-based biomarkers, and statistical methodologies to identify appropriate subpopulations. With these technologies, the

[4] Quintiles. The New Health 2012 Report: Rethinking the Risk Equation in Biopharmaceutical Medicine. Available at: http://newhealthreport.quintiles.com/wp-content/themes/new_health_report/media/pdf/Quintiles_NewHealthReport_2012.pdf

patients who are most likely to benefit can be identified, optimizing the benefit-risk profile. However, we need FDA's continued acceptance and support of stratifying biomarkers as valid inclusion criteria and Congressional support of collaborative efforts to combine and study existing genomic data, and to encourage ongoing banking of samples.

c) **Higher-quality study sites to limit variability**. Smaller studies in stratified subpopulations intensify the need for research precision exceeding currently accepted levels. In order to limit variability, the accelerated pathway will require higher-quality study sites than are currently required for traditional studies. This could undermine the validity of smaller stratified trials. Collaborations with investigators and the use of sites that exceed existing quality and operational metrics will be necessary. Specialized sites are increasingly being used in clinical research. Others commenting to the Committee have called for the creation of Clinical Trial Networks that meet agreed upon standards. Quintiles supports this concept, yet suggests that Congress consider existing networks and standards established through current private sector initiatives. For example, Quintiles has a Prime and Partner Sites program that identifies and partners with sites and investigators who are capable of delivering these enhanced research capabilities, and monitors their performance with metrics and ongoing review.

d) **Real-world drug use in approved subpopulations**. Registries can be used to evaluate the efficacy and safety of a new therapy in the narrowly defined subpopulation in routine clinical practice for which safety and efficacy have been demonstrated in pre-registration studies. Observational studies can be used to assess real-world efficacy of the drug in all patient populations, even those not specifically evaluated in pre-registration studies. In our experience, the combination of well-constructed registries and scientifically rigorous observational studies augments insights gained from prospective pre-registration studies. It also provides knowledge about the benefit-risk profile of a drug in the real-world setting most relevant to practicing healthcare providers and patients.

e) **Monitor use of medicines in patients not participating in registries** to identify and evaluate off-label use. Prospective observational studies based on EMRs could be conducted to monitor medicine use in patients who are not enrolled in registries or observational studies. This would provide insight into the real-world use of the therapy and help to assess the percentage of prescriptions that are consistent with the labeled indication, the ways in which patients who utilize a drug off-label differ from the population for which the drug was approved, and the outcomes in such patients.

All the necessary pieces are in place to embrace alternative pathways for drug evaluation and approval. The tools and data required to identify and monitor patients correctly exist now. An integrated approach to the continuum of development and prescribing can be identified. To borrow from the technology world, we must "think big, start small, and scale fast" to make this alternative pathway a reality so that patients in need can benefit without delay. Congress should clarify, and if necessary amend, FDA statutes to allow and encourage the agency to adopt new pathways for development of new medicines, biologics and devices (rather than defaulting to an up or down vote on 'safe and effective').

2. Master Protocols and Adaptive Designs

The Challenge

Clinical trial productivity is dramatically reduced and costs are vastly increased by the need for each Sponsor to conduct separate development programs in the same population for the same indications, for similar molecules or for molecules with common pharmacological mechanisms of action. Drug development failure rates are high, time is wasted with duplicative efforts, and patient participation is not optimized.

A Solution

Various study design approaches that identify failures faster and advance promising drugs are available, including Adaptive Designs and Master Protocols.

Adaptive Trial Design: There are many types of adaptive designs, but all such designs use Bayesian methodology to characterize drug efficacy more precisely and efficiently in selected populations, based upon cumulative experience. It is also possible to combine adaptive design within Master Protocols, such that multiple drugs can be simultaneously evaluated, such drugs "rolling in" or "rolling off" as available for study and as evaluation is completed. This approach is currently being evaluated for wider adoption by the EMA. The national regulatory authority in Singapore has similarly investigated the use of adaptive authorization within Master Protocols.

The I-SPY 2 trial is an example of an adaptive trial using a Master Protocol, being carried out by a consortium involving industry and academia, with the collaboration of the FDA. I-SPY 2 takes an agile approach, using a Master Protocol in which multiple oncology agents are evaluated in similar populations, with predefined success criteria, using a Bayesian adaptive design. The trial is for women with newly diagnosed locally advanced breast cancer segregated into treatment arms based upon biomarkers and other criteria. The study is evaluating whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone before having surgery, using complete radiographic response/remission, rather than event-free survival as the efficacy endpoint. The trial is simultaneously testing multiple investigational drugs thought to target the biology of each participant's tumor. If the data is supportive that a particular drug is may prove effective in a given patient subpopulation, this "proof of concept" study can form the basis for a subsequent Phase III trial, in which confirmation of response on this same radiographic endpoint can form the statutory basis for approval. The Sponsor must, however, commit to continuing the trial in order to assess the effects of the drug on event-free survival and to obtain broader labelling claims. Dr. King Jolly, Senior VP of Quintiles, serves as a member of the Executive Steering Committee of this trial, and has helped formulate operational, scientific, and regulatory strategies related to this program. Quintiles is also providing the traditional Clinical Research Organization (CRO) services for this trial, and has provided financial support.

Master Protocols: A Master Protocol allows multiple drugs to be evaluated in the same trial, with inclusion criteria that are relatively homogenous, and any necessary customization based on drug characteristics. Multiple compounds for a particular indication can be tested within the same Master Protocol, rather than requiring a separate protocol/development program for each. Only one placebo-controlled arm would be required instead of duplicating the same arm for each drug. This standardized, progressive regulatory approach would require fewer patients be on placebo and fewer enrolled overall, and significantly reduce costs and timelines by not requiring separate start-up and recruitment processes for different therapies.

Recommended Approach

Quintiles recommends encouraging the use of adaptive designs and Master Protocols to maximize identification of drugs that work in the patient population without having to duplicate efforts across multiple Sponsors. Congress could consider requiring a certain percentage (perhaps 10%) of therapies entering Phase II to include Master Protocols and adaptive designs and that regulatory standards and approval criteria be clarified to encourage multiple biopharma companies to collaborate on Master Protocols with Bayesian designs.

3. Reducing Today's Clinical Trial Timelines – Standardize and Harmonize

The Challenge

It is well documented that clinical trials are taking longer, and are becoming more complex and thus more expensive. The entire site start-up process, from Ethics Committee/Institutional Review Board (IRB) approval through site contracting can take up to 18 months. This must be completed before recruitment may begin. Ethics Committee approvals are a major delaying factor in clinical trial start-up; it can take up to a year to get approval to use a site, such as a hospital or medical practice. At present, for a 200-site study, the protocol is typically reviewed 200 times (once by each site) and 200 contracts are separately negotiated. The fastest timelines Quintiles typically sees for centralized IRBs are 45 days to approval vs. 105 days each with local, individual IRBs. Other factors delaying start up include not enough standardized clinical trial documentation, which leads to 'reinventing the wheel' for each study and often each site and the fact that there is currently much duplication of effort in regulatory filings, and sometimes trial criteria, between the United States and the EU.

Solutions

Below are short-term pragmatic solutions that would help improve trial timelines and reduce unnecessary duplication of effort and thus cost:

Centralized Ethics Committee Approvals: Our experience show that central IRBs, whose job is to perform this function, are two to three times faster at providing protocol review and approval to proceed.

Recommended Approach: Congress should urge the FDA to strongly encourage the use of central IRBs for the initial protocol review at the IND (investigational new drug) approval meeting – so that once a protocol has been approved by a recognized central IRB, it would effectively be approved for any site in the United States. Subsequent reviews at the site level IRB would focus on the specific requirements of each individual site (local regulations, and factors related to patients and investigators), but would not revisit the protocol and hold up the initiation of the other activities needed to get the trial up and running. Centralized IRBs are already used successfully in Europe, and a centralized process has also been implemented in hospitals in Quebec, including templates for informed consent paperwork.

Standardization of Clinical Trial Data and Documentation Requirements: Standardizing clinical trial data and documentation requirements, including qualifications for sites and IRB approvals, and informed consent forms would expedite the site start-up timeline. Investigator contract negotiation is also a time-consuming process with scope for added efficiencies. In Europe and other regions, these forms are approved by the regulatory authority as part of the clinical trial protocol review, with only minor changes being made at the site level.

Recommended approach: Congress should encourage the adoption of a harmonized set of standards that would result in a process that is less expensive and more iterative, making use of electronic systems and decreasing the paperwork involved. There are existing models and options that could be built upon to expedite this process, including collaborative private-sector efforts in the U.S. and approaches in other countries. The Clinical Data Interchange Standards Consortium (CDISC), an organization we helped found and which our President of Clinical Development Paula Brown Stafford currently chairs, has established widely-regarded standards to support the acquisition, exchange, submission and archive of clinical research data and metadata.

Harmonizing Regulatory Requirements Internationally: Today's drug development is a global endeavor. What determines where drugs are tested and made available is often complicated and made more expensive by varying requirements for studies across geographies, including between the U.S. and EU. For instance, preparing different regulatory authorization applications for each country, for the same studies, requires enormous staff time and thus cost, with little benefit or meaningful differences. At times, different requirements for studies can even lead to the discontinuation or significant delays in advancing of promising development programs due to the prohibitive cost of doing large-scale studies differently for different authorities.

Quintiles has particular experience of the need for harmonization, having seen introduction of a promising program for a rare disease slowed by several years because one region required a trial with a placebo arm, the other (where a competitor product was marketed) required a trial including standard of care. Given the limited population for this investigational therapy, there were not enough patients to carry out both a placebo controlled and a non-placebo controlled study in a timely manner. This resulted in significant delay in making the drug available to patients and unnecessary cost of running separate studies.

Increased harmonization would reduce redundancies that have significant time and cost implications, and improve availability of medicines for patients who need them.

Recommended Approach: There has been a gradual move towards more harmonization through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); this could be expanded and accelerated. The U.S. should increase cooperation and harmonization with other countries, starting with the EU, and consider mutual recognition of new drug regulatory authorization applications in the U.S. and EU. Congress should consider adding a goal to PDUFA 6, setting milestones for increased harmonization.

4. Improving Data Collection and Accessibility to Accelerate the Transition from "Analog to Digital" Drug Development

The Challenge

The practice of medicine and evaluation of therapies is a continual process that has largely been an experience- and paper-based endeavour. Today's technologies offer greater opportunities to harness real-world data and perform advanced analytics to inform better medical decisions, identify new uses and cures, improve drug development timelines and success rates, and more. While there are many efforts and advances, more can be done to truly harness this value.

As the white paper points out, analyzing data from the delivery setting could improve Discovery, Development and Delivery of better treatments. Below are examples of the benefits of data analytics

across the spectrum. Each of these is conducted today in varying degrees, but the accuracy and power of the insights are only as good as the data available for analysis:

Real World Data Drives Discovery	**Real World Data Improves Development**	**Real World Data Improves Delivery Decisions**
Improve understanding of disease and inform the next generation of development by identifying unmet needs and opportunities	Inform better study design, dosing, inclusion/exclusion criteria	Discover potential safety and interaction issues of approved therapies (which supports more aggressive approvals)
Identify new uses of approved therapies and support product extensions	Accelerate trial execution through integration with EMRs, with collection of data at point of care	Continually assess benefits and risks to inform better coverage and medical care decisions that reward value (cost *and* effectiveness)
	Accelerate patient recruitment through EMRs, social media, and internet-enabled patient portals that facilitate more rapid identification of patients suitable for clinical trials.	

A Solution

To achieve these benefits, public and private entities alike must continue to enable the evolution of clinical trial design and conduct from the traditional "analog and local" model to a "digital and global" one. This includes continued investment in technologies, expedited validation and use of new tools, and importantly, improved collection and accessibility of data.

In the **analog and local model** that is largely still the norm today, design and planning are based on individual experience, with patient recruitment depending on individual relationships. Finding the right patient is rather a hit and miss affair. Clinical trials are conducted with separate paper report forms that require duplicate entry of each visit (data in the clinician's usual patient care notes and then in clinical trial records) and rigid schedules. Before the adoption of electronic databases and analytics, interim data were not available for months at a time, and with conclusions drawn after biostatisticians combed through spreadsheets. Safety is demonstrated only through a large number of patients enrolled in studies. Clinical development programs are determined based upon regulatory precedent, the guidance from Key Opinion Leaders, and the experience of treating physicians.

In contrast, in a **digital, global model**, which the industry is making some small strides toward, design is informed by real-world large, de-identified datasets and performance and productivity metrics, with patient recruitment taking advantage of the Internet and social media. The right patient would be identified by prescreening through data collection instruments served through the Internet, and trials would be conducted by collecting data directly from EMRs or through data collected at point of care that is integrated with EMRs. Data would then be housed within HIPAA-compliant e-Source archives, accessible for real-time access, remote monitoring, and application of signal detection analytics to allow "just-in-time" assessment of safety and protocol compliance. Interim data would be available within hours, and safety demonstrated through immediate access to real-world data. Clinical development, in effect, would be EMR-enabled.

Recommended Approach

To maximize benefits of technology and analytics to further public health there are varying steps Congress could take to improve the quality and accessibility of data, listed below in order from ideal to step-wise improvements:

Create a central repository of accessible securely de-identified patient-level data and make available for research use through appropriate licensing. This would speed discoveries and development and improve assessment of real-world safety in larger populations. It would be a bold step, but others – such as the UK National Health Service – have made this a public health priority, and are gaining benefits from data that have been adequately anonymized and 'de-risked.' Currently, there are many large stores of patient data that can be de-identified, but the risk of being associated with, or liable for, the re-identification of individual patients hampers the willingness of care networks to share data with external researchers and causes reluctance among sponsors to work with third parties to tap the data. There is a need for a source of de-identified patient data to allow outcomes to be tracked, allowing use of real-world post-marketing data to answer regulatory approval questions. Regulatory changes could be made to provide a safe harbor for use of de-identified real-world patient data.

Other steps that could lead to improvements, short of the central repository described above, include:

Unique Patient Identifiers: Unique, HIPAA-compliant patient identifiers that follow individuals across settings, care networks, multiple EMR and health information systems would enable more accurate and comprehensive tracking of treatment outcomes and disease prevalence, which would help post-marketing surveillance, inform treatment options, identify treatment gaps and provide information to improve new drug development and clinical trial design and recruitment. At present, patient records and outcomes data may appear in many different places – including records from hospitals, pharmacies, ambulatory care centers, and death certificates – making accurate assessment of outcomes unattainable. A unique patient identifier would allow for easy decoupling of patients' identities and their record, protect privacy and reduce the disjointed nature of current systems and the duplication of identifying and de-identifying data as it is cleaned for research use.

Integration of EMRs: All EMR systems in the U.S. should ideally be interchangeable to allow a free flow of longitudinal health data accessible by everyone. This would allow real-world outcomes to be discerned much more quickly, allowing risk/benefit assessment to be carried out on millions of patients in near real time. This would transform the way we do clinical trials, giving access to patient data from all sources – doctor's office, urgent care, pharmacy clinics, hospitals, secondary, tertiary care centers – allowing complete tracking of patient care and outcomes. The Partnership to Advance Clinical electronic Research (PACeR) initiative[5] is aiming to standardize data across multiple EMR systems, and to implement clinical trial data collection systems that "wrap around" EMRs, allowing continuity of care across all locations. CDISC has an initiative underway in this area and is a member of PACeR. The government of Singapore has a mostly-uniform, countrywide uniform EMR system with a lot of interchangeability, allowing comprehensive assessment of safety data and outcomes. This has given the regulatory authorities the confidence needed to approve products for narrowly defined populations from smaller trials, followed by additional, larger trials to expand the label (adaptive or staggered licensing/approval).

[5] http://pacerhealth.org

Improved Data Standards/Integration to unlock the power of real-world late phase data: Improved data standardization and integration is needed, as is the ability to contact patients directly via digital communities. There is scope for standardization of Electronic Data Capture (EDC) formats, which at present are different in each company. Standards should be established for data that are gathered iteratively and are common to every trial, such as safety, demographics, pharmacokinetics and clinical pharmacology, and in some cases, therapeutic standards. EMRs are most useful in integrated delivery systems. In the U.S., there are many different EMR vendors/systems, and they are used in various permutations. For the most part, such systems are not interchangeable; nor are they configured for clinical trials. Quintiles has put together the COMPASS Distributed Data Network[6] of around 10 EMR systems covering 19 million people for studies, and this is proving useful for safety and outcomes research. Another useful approach is to carry out hybrid studies using de-identified data from EMRs, supplemented by more focused data collection the physician and the patient. This approach allows better clinical trial functionality from EMRs. Safety and adverse event (AE) reporting could be stimulated using an add-on patch to the EMR, giving the physician the option to report that a symptom may be related to a drug; if yes, a link could pop up to MedWatch.

Use of Social Media and the Internet in Drug Development: Social media has changed the doctor-patient relationship and is fuelling the rise of patient empowerment. Online communities for sharing of information about disease symptoms, medication side-effects and clinical outcomes have become commonplace. Many entrepreneurs and established companies – and the government – are leveraging these networks to inform their development strategies, and even to identify and recruit patients. For example, Quintiles' Mediguard.org and ClinicalResearch.com support a community of patients who have opted to provide medication and condition information and are motivated to participate in research. Currently, over 2.6 million patients in the U.S., UK, France, Germany, Spain, and Australia have registered making it one of the largest and fastest-growing healthcare communities in history. Social media-based interactions of this kind represent a disruptive technology that can harness large, de-identified datasets. There is potential for a new research paradigm for data collection, adverse event reporting and even direct-to-patient recruiting for clinical trials, and social-media based trials. Potential benefits for clinical trials are far-reaching, including lower cost and high speed versus traditional site-centric model, better connectivity between multiple healthcare stakeholders, reduction of geographical limits, and the potential for long-term contact and participation.

Looking ahead, social media could accelerate timelines and reduce the costs of drug development in some diseases, with the potential to contact motivated patients directly, rather than working through the complexities and expenses of site contracting. The advent of a social media based trial is not unthinkable, and this is a truly disruptive force in healthcare. As with traditional trials, though, high data quality will be essential. The policy issue for today is to ensure adequate data protection and patient safety – including provisions for informed consent – without 'handcuffing' patients' ability to 'opt in' to research in the public forum of the Internet. Congress needs to protect such clinical trial participants from discrimination or other harms based on what they reveal online. The fact that pre-existing condition exclusions for health insurance are now prohibited is a step in the right direction.

Sharing of Precompetitive Data: It would be helpful if precompetitive data of no direct commercial value – including placebo data, safety and other data, data related to products that have failed and are no longer being developed, and data on products that are off patent – could be made available for modelling and simulation of trial outcomes. This could improve the probability of trial success for all

[6] http://www.quintiles.com/assets/0/111/118/233/1338/d098e5fb-d882-475d-b305-8865c2131aae.pdf

Sponsors. For example, under the new openFDA initiative the FDA is making public millions of reports about prescription medicines, such as adverse events and medication errors, between 2004 and 2013. The FDA has also done some work to encourage companies to submit genomic data associated with their early development programs to add to the general body of knowledge. More data would allow validation of additional tools.

Each of these approaches would help in varying degrees to improve the quality and availability of data, and would in turn improve discovery, development and delivery of new cures and improved treatments for patients. With the data and analytical tools available today, we already see the value in terms of improving design, predictability and achievement of patient enrolment and ultimately improving probability of success. In the post-marketing phase, as data and techniques improve, there is tremendous potential for insights to improve care, identify new uses and assure safety. Congress should work to encourage the integration and accessibility of data, within the bounds of patient privacy.

We believe that action on the four highlighted focus areas – alternative development pathways, Master Protocols and adaptive designs, standardizing and harmonizing, and improving data collection and accessibility – would fuel continued advancement of clinical research and patient care from analog to digital, and from the 20th Century to the 21st.

Respectfully submitted,

Dr. Derek Winstanly
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American Academy of
Allergy Asthma & Immunology

STATEMENT OF THE AMERICAN ACADEMY OF ALLERGY, ASTHMA AND IMMUNOLOGY

TO THE
HOUSE COMMITTEE ON ENERGY AND COMMERCE

on the

21st Century Cures Initiative

June 13, 2014

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The American Academy of Allergy, Asthma and Immunology (AAAAI) is a professional organization of more than 6,000 members. Our membership includes allergist/immunologists, other medical specialists, allied health and related health care professionals who focus on research and treatment of allergic and immunologic diseases. The AAAAI applauds the Committee's effort to examine ways to accelerate the pace of biomedical discoveries and to bridge the gap between the laboratory bench and the patient bedside. Following are the Academy's responses to a number of the questions raised in the Committee's May 16, 2014 request for comments.

What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

Allergen Immunotherapy: Often referred to as "allergy shots," allergen immunotherapy (AIT) has the potential for curing allergic rhinitis and the allergic component of asthma. It involves a long-term treatment that decreases symptoms for many people with hay fever, allergic asthma, eye allergy, or stinging insect allergy. Unlike more expensive symptomatic treatment, AIT modifies the allergic disease. While traditionally involving regular injections, there has been significant progress in the development of sublingual immunotherapy in recent years. In April, the FDA approved the first sublingual tablets for the treatment of grass and ragweed allergy. Researchers are engaged in testing approaches to potentially groundbreaking immunotherapy for patients with food allergy as well. In short, this 100-year-old therapy is now the focus of very exciting, transformative developments.

Despite the known clinical effectiveness of AIT, studies have shown that it is severely underutilized. The Academy is pleased that the National Institute of Allergy and Infectious Diseases (NIAID) is working with the Agency for Healthcare Research and Quality to convene a workshop of experts on AIT in 2015. Progress toward improved treatment for asthma and allergic diseases can be made if the research recommended by such a panel is funded.

Food Allergy: In the area of food allergy, the only effective treatment is avoidance. The most promising research is in the area of immunotherapy, which has been shown to have a beneficial effect on the amount of the allergenic food that is tolerated without inducing severe reactions. Clinical trials are pursuing various strategies, including topical, oral and sublingual immunotherapy, as well as testing monoclonal antibodies as additional strategies to improve safety of immunotherapy for food allergy. Again, the NIAID has been the principal sponsor of research on food allergies. The NIAID has also developed clinical guidelines for the diagnosis and management of food allergies.

As recently as 2003, the NIH spent less than $2 million on food allergy research. Today, over $25 million is allocated. While this growth has been impressive, it is important to note that approximately 15 million Americans suffer from food allergies. It would be difficult to identify another disease affecting such a large population toward which NIH dedicates such a minute fraction of its budget. Limited funding is slowing progress toward a treatment for food allergies.

Asthma: Major advances have been made in identifying differences in asthma from patient to patient; differences that predict severity and morbidity; and methods to more effectively identify those at greatest risk for asthma attacks. An important focus is asthma in the African American and Hispanic populations, since asthma affects these groups disproportionately in terms of both frequency and severity. Basic research discoveries must be translated to determine which treatments will be most effective for those patients at greatest risk.

In October of 2013, the National Heart, Lung, and Blood Institute (NHLBI) held a workshop on the primary prevention of asthma. The report of that workshop recommends basic and clinical research to test asthma prevention strategies. Funding for such initiatives could result in significant reduction in the prevalence and high cost of asthma.

The NHLBI has published guidelines for the diagnosis and management of asthma. Efforts to reduce asthma exacerbations and death depend on research to develop methods of improving physician and patient adherence to these guidelines.

Drug Allergy: Allergic reactions to medications are a serious medical problem. Inability to tolerate antibiotics and aspirin complicate care for routine medical problems. In addition, patients experience allergic reactions to drugs for debilitating and potentially fatal diseases including cancer, HIV/AIDS, cystic fibrosis, and rheumatoid arthritis. In early 2013, the NIAID sponsored a workshop to develop a research agenda on the diagnosis and management of patients with drug hypersensitivity. Minimal NIH funding is dedicated to this problem. Progress will not be made unless an initiative to implement the research recommendations of the 2013 workshop is developed and funded.

Eosinophil-Related Disorders: Eosinophilic disorders occur when eosinophils, a type of white blood cell, are found in above-normal levels in various parts of the body and trigger chronic inflammation that can result in tissue or organ damage. In some cases, this results from an allergy-triggering food or airborne allergen. There are no effective treatments for these diseases. For many patients with eosinophilic gastrointestinal disorders, it is impossible to eat normal foods, forcing a reliance on elemental formula or GI tube feeding. Under the leadership of the NIAID, the NIH convened the Task Force on the Research Needs of Eosinophil-Associated Diseases (TREAD).

Members of the House and Senate Appropriations Committee have strongly encouraged the NIH to implement a multi-Institute, multi-disciplinary research initiative on eosinophil-related disorders. Progress in this area depends on funding for this effort.

Immunologic Diseases: Primary Immune Deficiency Diseases (PIDDs) affect approximately 500,000 people in the United States. Such diseases are associated with significant morbidity and mortality, especially in early childhood. The development of targeted immune-based therapies has been shown to favorably treat and alter the progression of some PIDDs. Transplantation is another approach that has demonstrated success. However, these therapies are associated with adverse effects. New, more focused therapeutic strategies are in development. Additional research is needed to better understand and refine these and other approaches to the care of PIDDs.

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?

Since it was founded by the Academy in 1993, the Allergy, Asthma, and Immunology Education and Research Trust has provided almost $5 million to support 80 junior and established investigators in our field. The Academy interacts closely with Food Allergy Research and Education; the American Partnership for Eosinophilic Disorders; the American Lung Association; and other patient groups dedicated to serving patients and funding research. The Centers for Medicare and Medicaid Services (CMS) has approved the AAAAI Allergy, Asthma & Immunology Quality Clinical Data Registry as a Qualified Clinical Data Registry (QCDR). The focus is quality measures for allergy immunotherapy and asthma. Data from the registry can be used to analyze approaches to improving the quality of care for these conditions.

What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

The major barriers to advancing breakthroughs in our field and others are: 1) the shrinking population of active physician scientists, particularly those focused on patient-oriented research; and 2) the difficulty of getting translational research funded by the NIH. In 2000, the Congress enacted the Clinical Research Enhancement Act to address these problems, but the programs authorized in that legislation are inadequate to the challenge of ensuring that the NIH rescues the clinical investigator from becoming an endangered species, as first described by NIH Director James Wyngaarden over three decades ago. The Academy encourages the Committee to

examine this issue as perhaps THE most important barrier to progress toward cures and new therapies. A major program should be implemented through which NIH funds the patient-oriented, bench-to-bedside-to-bench research that is necessary for medical innovation.

***What is the financial burden of your disease? How would better treatments and cures help* save money for your family and the federal government?**

Asthma and allergic diseases affect 1 in 5 Americans. The annual cost of asthma is estimated at $18 billion, and asthma is the fourth leading cause of work absenteeism. Among children age 5-17, asthma is the leading cause of missed days from school.

Allergic rhinitis (hay fever) is the fifth most costly chronic disease in the U.S, with total direct costs estimated at $11.5 billion.

Food allergies account for an emergency room visit every three minutes in the United States. Food allergies affect about 8 percent of children in the United States at a cost of $25 billion including medical care, family expenses, special diets and allergen-free foods.

For additional information on this statement, please contact Lynn Morrison at [redacted]

The Coalition for

Pediatric Medical Research

fightsma

June 13, 2014

The Honorable Fred Upton
Chairman
Committee on Energy & Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight & Investigations
Committee on Energy & Commerce
2322A Rayburn House Office Building
Washington, DC 20515

VIA ELECTRONIC DELIVERY

Dear Chairman Upton and Rep. DeGette:

The Coalition for Pediatric Medical Research, an alliance of many of our nation's leading children's hospitals and research institutions, and FightSMA, a national organization of families working to find a treatment for spinal muscular atrophy (SMA), applaud you for launching the 21st Century Cures Initiative. As you noted in introducing the initiative, such a comprehensive look at the multiple components of our research and development infrastructure – public and private – is urgently needed. **We are writing to urge that you strongly consider convening a roundtable, hearing or related session focused on the unique needs – as well as the opportunities – in the pediatric research sector that must be addressed to improve the health and well-being of our nation's children.**

The Coalition and Fight SMA wish to thank you for enacting into law the National Pediatric Research Network Act, Title II of the PREEMIE Reauthorization Act (Public Law 113-55). As you referenced in your third white paper focused on patients, the NPRNA is one of the recent "bipartisan solutions" the committee has enacted to "facilitate and accelerate patient access to innovative treatments." If fully implemented as envisioned, the NPRNA has the potential to accelerate the cycle of discovery from basic research through clinical trials, greatly enhancing our ability to successfully treat thousands of devastating pediatric diseases and conditions.

The NPRNA was born out of a collective frustration with the disproportionately low levels of support that have historically been dedicated toward pediatric research – public and private. More than 50 years ago, the landmark Cooke task force issued a report indicating that the nation's pediatric research commitment was largely non-existent. In 1962, Congress responded to the Cooke task force by establishing the NICHD, though pediatric research is supported by many other institutes and centers throughout the NIH. The NPRNA articulates a vision of the entire pediatric research community – academic researchers, clinicians, patient advocacy organization, and others – working day-in and day-out to achieve the scientific breakthroughs needed to develop new treatments and therapies and accelerate their delivery to patients in need. While research is challenging across the board and in all populations, pediatric research faces particular challenges.

These include:

- The high costs associated with the core infrastructure – such as advanced genomics technologies, cell manufacturing and cell manipulating cores, biobanks, and DNA sequencing center – that are necessary to discharge cutting edge 21st Century pediatric research programs.

- The reality that many pediatric diseases and disorders are rare diseases affecting fewer than 200,000 persons. This presents several logistical and cost challenges for researchers studying diseases affecting such patients, particularly the ability to recruit the necessary number of subjects for studies, including clinical trials. The solution is often found within multi-institution collaborations able to cumulatively recruit adequate patient populations.

- Given relatively small disease populations, pediatrics has historically faced challenges competing for funding and other resources against researchers and institutions focused exclusively or primarily on conditions that onset in adulthood.

While pediatrics focuses on a clearly defined period of life, it is important to note that a number of diseases that manifest later in life, such as diabetes, hypertension and heart disease, can be rooted in the pediatric years. And, for those diseases that manifest in the pediatric years, several can be life-long and require intensive and high-cost interventions. A robust commitment to pediatric research and discovery, therefore, can yield immense benefits well beyond the childhood and adolescent years.

Given the importance and unique nature of these issues, we are writing to strongly encourage you and your colleagues to convene a roundtable or hearing focused specifically on the unique issues of pediatric research. Such a session, including a pre-session white paper, could thoroughly probe the challenges and opportunities in the space and help support robust implementation of laws like the NPRNA and others. It should ideally include a range of stakeholders including:

- Children's hospitals and related research institutions caring for our children and working every day to develop new therapies and treatments;

- Patient advocacy organizations who give voice to the needs of defined populations and who fund increasing amounts of the research agenda; and

- Biopharmaceutical and medical device manufacturers and investors, particularly those focused heavily in the pediatrics sector, who can speak to the regulatory and market challenges.

To develop a pediatric-focused component of the 21st Century Cures Initiative, the Coalition and Fight SMA would like to request a meeting with you and your staff at the earliest convenience, and we will be in touch with your offices in the near future to work on arranging a meeting.

Thank you, again, for your longstanding leadership on pediatric research issues and for leading this much-needed undertaking.

Sincerely,

/S/
Nick Manetto
For the Coalition for Pediatric Medical Research

/S/
Steven Eichenauer
For FightSMA

DEADLIEST CANCERS COALITION

June 13, 2014

The Honorable Fred Upton
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette
2368 Rayburn House Office Building
Washington, D.C. 20515

Sent via e-mail: Cures@mail.house.gov

Re: Request for Information Regarding the 21st Century Cures Initiative

Chairman Upton, Representative DeGette:

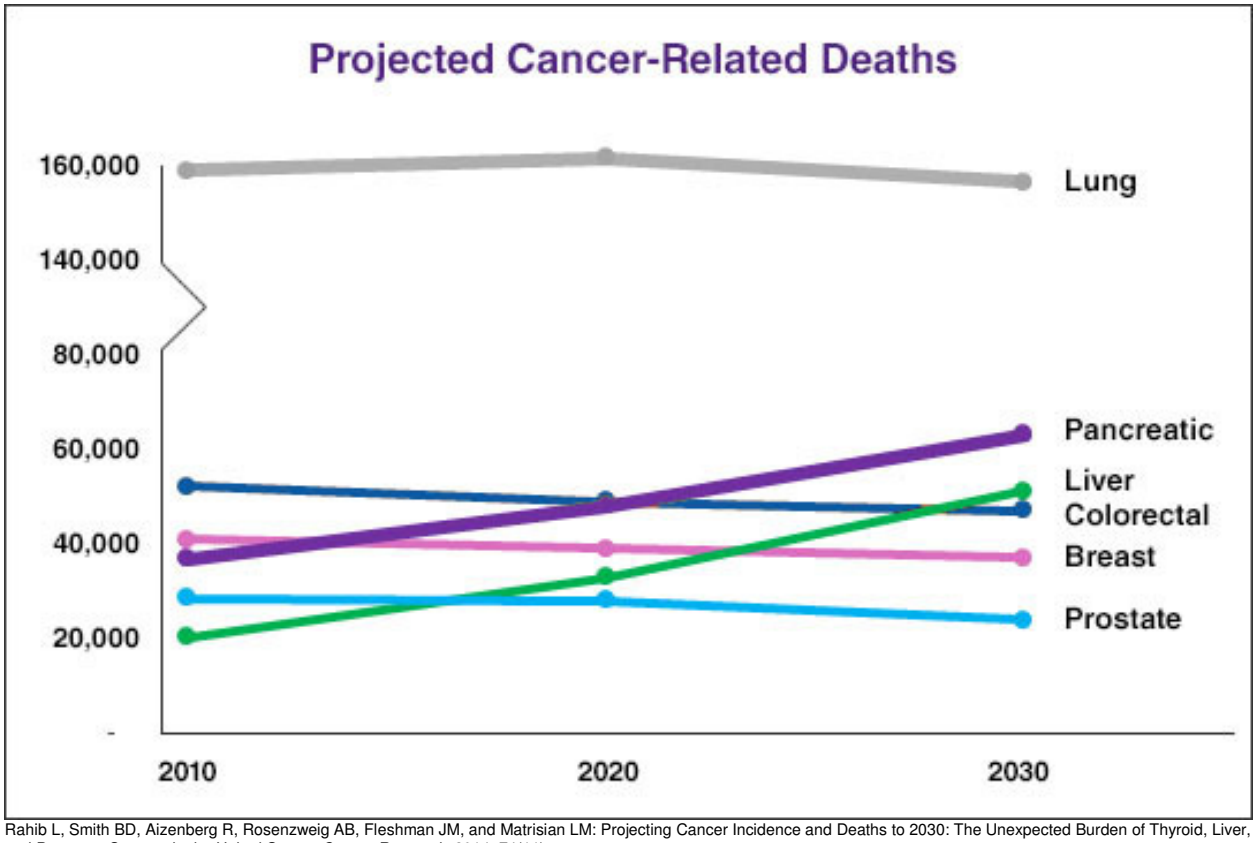
On behalf of the Deadliest Cancers Coalition, a collaboration of national non-profit organizations focused on addressing policy issues related to our nation's most lethal cancers, we thank you for the opportunity to provide input to the *21st Century Cures initiative*. As was noted by Margaret Anderson, Executive Director of FasterCures, at a recent 21st Century Roundtable, "There are 7,000 known diseases. We have treatments for only 500 of them. We have work to do."

Nowhere is that gap more evident than when it comes to the deadliest cancers or recalcitrant cancers, which are defined in the *Recalcitrant Cancer Research Act of 2012* as those cancers with five-year relative survival rates below 50 percent. While there are various types of cancers that fall under this definition, it is worth noting that nearly half of the 585,000 cancer deaths expected in 2014 will be caused by eight site-specific cancers: brain, esophagus, liver, lung, myeloma, ovary, pancreas and stomach.

Receiving a diagnosis of any type of the more than 200 different cancers is devastating. Being diagnosed with a deadly cancer is particularly horrific. Instead of talking to their physician about treatment options, patients diagnosed with a deadly cancer are frequently told to go home and get their affairs in order. For these patients, research is the **only** hope.

The prospects for many of the deadly cancers are only getting worse. The likelihood of being diagnosed with gastric cancer between ages 25-39 has increased unexpectedly by almost 70 percent since 1977. Further, a recent report published in *Cancer Research* predicts that pancreatic cancer will surpass breast and colorectal cancer to become the second leading cause of cancer-related death by 2020. Liver cancer will replace prostate cancer to become the fifth leading cause of cancer related-death that same year.

The same report also predicts that by 2030, the top five cancer killers in the U.S. will be lung, pancreatic, liver, colorectal and breast – a dramatic shift from the current ranking of lung, colorectal, breast, pancreatic and prostate. Lung, pancreatic and liver cancers are all considered to be deadly, or recalcitrant, cancers. Their rise in the rankings of cancer killers underscores the need for a greater federal research investment to prevent these predictions from coming true.



Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, and Matrisian LM: Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. *Cancer Research*, 2014; 74(11).

We know that investment in medical research makes a difference. Indeed, it was the key to the significant strides that have already been made against many forms of cancer—

- Today, there are nearly 14 million cancer survivors living in the U.S., 15 percent of whom were diagnosed 20 or more years ago.
- There have been more than one million fewer cancer deaths since the early 1990s as a result of screening, early detection tools and improved treatments.
- More than 68 percent of adults are living five years or more after their initial diagnosis, up from 50 percent in 1975.
- The five-year survival rate for all childhood cancers combined increased from 58 percent in 1975-77 to more than 80 percent in 2013.

It is time that this same type of progress is made in our nation's deadliest cancers.

We should note that the Deadliest Cancers Coalition was organized on the principle that *all* cancer patients deserve at least a 50-50 chance of survival, and, *at a minimum*, survival from all types of cancers should be above the starting line that was established 30 years ago when the

overall cancer survival rate was 50 percent. Recognizing that there are a number of cancers that have not yet reached that starting line – and in most cases are not even close – Congress in December 2012 passed the *Recalcitrant Cancer Research Act* (Public Law 112-239), calling for a targeted effort to address the greatest challenges with the greatest need: high mortality cancers.

This bill, which was signed into law on January 2, 2013, calls on the National Cancer Institute (NCI) to develop scientific frameworks for pancreatic and lung cancer, blueprints which will help provide the strategic direction necessary to make true progress against these deadly cancers. At the NCI Director's discretion, scientific frameworks also may be developed for other deadly, or recalcitrant, cancers.

While research investment is critical, the Act recognizes that by tackling the hardest and most complex problems, we will likely see the greatest rewards for the entire field. If we hope to discover early detection tools and effective treatments, we must shine a bright light on the deadliest cancers.

The *Recalcitrant Cancer Research Act* represents an important first step towards that goal by calling on NCI to develop scientific frameworks for assessing and advancing research—frameworks that will help lead the way to scientific advancements, evaluate the sufficiency of researchers and outline a plan for ongoing research.

There is promise in the medical research field for many of these diseases. In fact, as a result of the *Recalcitrant Cancer Research Act*, the NCI has released a "scientific framework" report outlining priority areas of research focus for pancreatic cancer and is in the process of developing a similar report for lung cancer. These reports demonstrate the vast potential for progress in diseases that are currently feared as some of our nation's leading killers, however, that promise is being severely under-cut by the steady erosion of funding for the NCI. We believe that this innovative approach establishes a model for attacking other high mortality cancers by lending a greater degree of structure and accountability to the research continuum.

When accounting for inflation, the NIH budget has dropped 22% ($6 billion) since 2003; NCI's budget has been cut even more – 24.7% ($1.1 billion). Further, cancer research funding as a share of the NIH budget has declined. In the late 1990s, NCI's budget made up 18.7 percent of the NIH budget. Today, it is 16.4 percent of the NIH budget. That decline has reduced NCI's funding by $680 million below what it would have received in FY 2014 if its share of NIH's total budget had been maintained.

As you consider ways to accelerate the cycle of discovery, development and delivery of promising new treatments, we urge you to consider the special challenges associated with deadly cancers and to identify new approaches to target research on these diseases. We further urge you to support a robust budget for the NCI, including providing $5.26 billion for the NCI for Fiscal Year 2015.

If you have questions or need more information, please contact Megan Gordon Don at [redacted]

Sincerely,

The Deadliest Cancers Coalition

American Association for the Study of Liver Diseases
American College of Gastroenterology
American Gastroenterological Association
American Liver Foundation
American Pancreatic Association
American Society for Gastrointestinal Endoscopy
Asbestos Disease Awareness Organization (ADAO)
Debbie's Dream Foundation: Curing Stomach Cancer
Digestive Disease National Coalition
Esophageal Cancer Action Network (ECAN)
Hepatitis B Foundation
Hepatitis Foundation International
International Myeloma Foundation
Lung Cancer Alliance
Mesothelioma Applied Research Foundation
National Brain Tumor Society
National Ovarian Cancer Coalition
National Pancreas Foundation
Ovarian Cancer National Alliance
Pancreatic Cancer Action Network
Society of Gynecologic Oncologists
TargetCancer

National Brain Tumor Society

June 13, 2014

The Honorable Fred Upton (R-MI)
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette (D-CO)
Member
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Sent via e-mail: Cures@mail.house.gov

Re: Request for Information Regarding the 21st Century Cures Initiative

Dear Chairman Upton and Representative DeGette,

Thank you for your willingness to explore and improve disease discovery, development and delivery through the 21st Century Cures Initiative. As the largest nonprofit dedicated to the brain tumor community in the United States, the National Brain Tumor Society was encouraged to hear of your initiative and desire to effectuate policy change to support promising new treatments and cures. Your mission relates directly to ours: finding better treatments, and ultimately a cure, for people living with a brain tumor today and anyone who will be diagnosed tomorrow.

There are nearly 700,000 Americans living with one of the more than 120 different types of brain tumors, yet there have only been four (4) U.S. Food & Drug Administration (FDA)-approved therapies in the last 30 years. Sadly, the average survival rate for all malignant brain tumor patients is just 33.8%. Additionally, malignant brain tumors are the leading cause of cancer-related death for children under 10 years of age, and the second leading cause of cancer-related death in all children under 20 years of age. For the most aggressive pediatric brain tumors, chances of long-term survival are less than 20%. Adult and pediatric brain tumor patients desperately need expanded research, drug development and access to new, innovative treatments.

National Brain Tumor Society's strategic initiatives and funded programs aim to improve the brain tumor research enterprise in order to transform scientific findings into new and more effective treatments, as quickly as possible. To achieve these goals, we foster collaboration and change within all facets of the drug discovery and development landscape, and invest in key initiatives poised to deliver results. We look forward to working with you in the coming months and years to bring about better research and treatments. Thank you for the opportunity to share the following information in response to your request for comments published in the white paper entitled *21st Century Cures: A Call to Action*.

Discovery, Development and Delivery: A Collaborative Approach
From basic science to clinical trial designs, the National Brain Tumor Society partners with the world's leaders in research, public policy, and clinical care to advance the understanding of brain tumors, expand the availability of new treatments, and drive the discovery of a cure. With targeted programs for both adult and pediatric brain tumors, as well as other strategic initiatives to improve access and approvals of newfound discoveries. We drive bold, innovative programs to ensure a brighter future. The information below will provide you with an overview of some of our current initiatives.

Defeat GBM Research Collaborative
We believe it is our duty to drive the advancement of research in the area of adult GBM (glioblastoma multiforme), the most common and deadliest form of brain cancer, to understand how to combat its resistance and adaptability, and deliver new and effective therapies to improve patient survival. With this in mind, the National Brain Tumor Society recently launched the Defeat GBM Research Collaborative, a multi-faceted and concentrated effort, which aims to double the five-year survival rate of GBM patients in just five years. The unique aspects of this program are the simultaneous research efforts in basic

discovery science, translational science, pre-clinical drug development, and clinical trial design, all intended to quicken the pace of discovery, transfer knowledge to drug development, identify the right biological targets, and improve clinical trials.

Project Impact: Driving Discovery to a Cure for Pediatric Brain Tumors
National Brain Tumor Society is committed to directing one-third of its research budget to pediatric-specific initiatives, and has previously undertaken fruitful initiatives in both pediatric brain tumor molecular profiling and developmental neurobiology, which respectively made important contributions to the fields of pediatric brain tumor research and neuroscience. Our newest pediatric initiative, Project Impact, will leverage this knowledge, and develop a program to address interrelated barriers that are slowing drug development for pediatric brain tumors, specifically high-grade gliomas. One such barrier within the pre-clinical research arena is the lack of robust and reproducible models and tools needed for therapeutic development. Additionally working with the pharmaceutical industry, government and regulatory officials, and leaders in the pediatric neuro-oncology community, Project Impact will confront inefficiencies including regulatory impediments that currently exist in the pediatric brain tumor pre-clinical research system, and the entire pediatric cancer clinical trial environment.

Clinical Trial Endpoints Initiative
Our Clinical Trial Endpoints Initiative aims to establish, in collaboration with the FDA, accepted clinical trial goals and guidance that will incentivize the pharmaceutical industry to develop and deliver therapies that achieve better outcomes for the brain tumor community. National Brain Tumor Society worked alongside other patient advocacy and philanthropic organizations to create the Jumpstarting Brain Tumor Drug Development Coalition. This coalition has set forth to convene all the necessary stakeholders (medical imaging companies, biotech and pharmaceutical companies, neuro-radiologists, neuro-oncologists, contract research organizations, the National Cancer Institute, and the FDA) in two separate workshops to advance alternative endpoints for brain tumor clinical trials. The discussions and action items that come out of these workshops are meant to inform and guide the neuro-oncology and clinical trial sponsor community. It is our hope these changes will create more incentives for future research and investment in brain tumor treatments, and deliver a pipeline of new drugs to the community.

Policy Recommendations
The 21st Century Cures white paper asks the question of patient advocacy groups, “What can Congress do?” The following policy recommendations will address that question in the areas of brain tumor discovery, treatment development, and delivery.

Renewed Commitment to Medical Research Funding
Although our above initiatives aim to bring about increased discovery in the field of brain tumors, private [redacted] the key leadership role that the National Institutes of Health (NIH) plays in funding, coordinating, and advancing research. Critical research at the National Institutes of Health (NIH) is laying the groundwork for breakthroughs. The NIH is the largest funder of brain tumor research in the United States, and impacts the brain tumor community through many institutes including: the National Cancer Institute (NCI), National Institute of Neurological Disorders and Stroke (NINDS), National Human Genome Research Institute (NHGRI), and National Center for Advancing Translational Sciences (NCATS).

Therefore, we support robust funding of the NIH, including NCI. Congress should renew its historic, bipartisan commitment to the fight against cancer, including brain tumors, by increasing appropriations for NIH in FY 2015 to $32 billion, including an increase for NCI to $5.26 billion. Additionally, we hope that Congress will make regular increases to the NIH budget in the upcoming budget years to restore our country’s place as the global leader in biomedical research in the 21st century.

Pediatric Cancer Research & Development
Every year, more than 4,000 children are diagnosed with a brain tumor in the United States and, as noted above, malignant brain tumors are the leading cause of cancer-related death for children under 10 years of age. Congress can take action to increase the quality of research currently conducted in pediatric cancer.

Biospecimens and demographic information, which are vital for research, are not collected for over half of pediatric cancer patients, but are crucial to basic scientific research and drug development. Legislation has been filed that would address that problem, improve pediatric cancer research and achieve a greater understanding of the effects of treatments. **HR 2607**, **The Caroline Pryce Walker Conquer Childhood Cancer Reauthorization Act,** would require a report to Congress about the barriers to research and drug development. If passed, it would call for the collection of biospecimens and demographic information from 90% of pediatric cancer patients and provide access to a secure searchable database for healthcare professionals. Access to such vital statistics will help researchers achieve a better understanding of childhood cancers and the effects of treatments for such cancers. We hope that the Committee will increase its commitment to fighting pediatric cancer by supporting HR 2607 as part of the 21st Century Cures initiative

Supportive Environment for Drug Development & Approval
With only four (4) therapies approved to treat brain tumors in the past 30 years, we need a better clinical trial environment to accelerate the development and approval of therapies. Brain tumor patients don't have the luxury of time – they need more effective treatment options today. While we applaud Congress's passage of the Food and Drug Administration Safety and Innovation Act (FDASIA), including the provisions for Breakthrough Therapy Designation and the Caring Hope Act, we need to go further. Public policy should continue to create incentives for early involvement of the biopharmaceutical industry in rare disease and pediatric cancer drug development, which will advance safe and effective therapies for those with limited current treatment options.

As noted when discussing our Clinical Trial Endpoints Initiative, the U.S. Food and Drug Administration (FDA) is more committed than ever to jumpstarting brain tumor drug development by improving clinical trials, and no amount of private funding can replace the FDA's regulatory role in evaluating and approving new treatments. We urge Congress to provide an appropriation of $2.78 billion in FY2015 for the FDA, and maintain a high commitment to FDA funding in upcoming fiscal years.

Ensuring Affordability of Oral Chemotherapy for Brain Tumor Patients
While the discovery and development of new brain tumor therapies and a cure remains our top priority, those treatments will be useless if brain tumor patients cannot access them. As noted, there are very few therapies available for brain tumors patients. One type of chemotherapy, temozolomide (Temodar), is a widely used treatment, and often the standard of care for many patients with malignant brain tumors.

Temozolomide is almost exclusively prescribed orally and many private health insurance plans cover the treatment as a pharmacy benefit and not as a medical benefit, as traditional IV chemotherapy is covered. The result can be high co-pays or co-insurance in the hundreds or even thousands of dollars per month. [redacted] patients are reporting that they cannot afford the out-of-pocket costs per month to access temozolomide, yet they must access this medicine as part of their oncologist-prescribed brain tumor treatment.

For many brain tumor patients there is not an IV chemotherapy substitute. Thus, health insurance cost-sharing can create real economic hardships and present a barrier to the affordability of a medically necessary chemotherapy regimen. Additionally, research has found that more than 25 percent of all anticancer agents currently in development are planned as oral drugs. Many of these new oral drugs have shown significant clinical advantages over traditional IV/injected forms of cancer treatment in early trials. As new treatments come into the marketplace, the affordability of oral and other patient administered anticancer medications will become an even larger problem, both for patients as well as the pharmaceutical industry.

HR 1801, The Cancer Drug Coverage Parity Act, would require health plans to cover patient-administered chemotherapy on an equal basis as chemotherapy given through hospital administered IV or injection. Because it will only apply to health plans that already cover chemotherapy, this is not a mandate. Not only is access to oral chemotherapy critical to delivering the standard of care, it can be beneficial to the patient's quality of life because he or she can undergo treatment at home instead of traveling to a hospital. Health insurance should facilitate brain tumor treatment, not create a financial barrier to it. We hope that the Committee will support HR 1801 to guarantee that current and future innovative treatments are accessible for patients.

Coverage for Participation in Research at National Cancer Institute (NCI) Designated Cancer Centers
Recently, an issue has surfaced that could cause a major impediment to cancer research, as well as patient access to clinical trials. According to a report prepared by Milliman, Inc. and commissioned by the Leukemia & Lymphoma Society[1], many of the health plans that are participating in the insurance exchanges offer limited access to NCI-designated cancer centers, as they are not considered by the plans to be "in-network." In theory, the Affordable Care Act's expansion in coverage of care associated with participation in clinical research will not only lead to an increase in research, but will also result in better recruitment and access to alternative treatment options when patients exhaust already approved therapies. However, with much of this research occurring at NCI-designated cancer centers, it is of serious concern that many plans do not consider these state of the art centers to be in-network and will therefore limit potential research and patient access.

There are currently 68 NCI-designated cancer centers in the United States, where researchers are working to develop new technologies to prevent, diagnose, and treat all types of cancer. To earn this designation, these centers must meet rigorous criteria in multidisciplinary cancer research. For brain tumor patients, the research conducted at these top-level institutions is of vital importance and will lead to desperately needed new discoveries in the genetic and biological make up of tumors, as well as possible treatment options. Research relies heavily on the availability and use of biospecimens, including tumor tissue, to increase knowledge and develop innovative treatments and technologies. If NCI-designated cancer centers are deemed "out of network," patients will be forced to seek treatment at hospitals that are not equipped to properly resect, analyze, and store brain tumor tissue for research, and which do not offer patients the option to participate in a clinical trials. While the 21st Century Cures Initiative looks to promote innovative research, this policy will only deter it. We ask the Committee to address this impediment to research and encourage the inclusion of NCI-designated cancer centers in exchange plans.

Conclusion
On behalf of the brain tumor community, thank you for taking on the important task of the 21st Century Cures initiative. We greatly appreciate the opportunity to provide input on ways to improve discovery, development, and delivery of new, innovative treatments, and look forward to partnering with the Committee on this goal. If we can be of assistance at any time as you continue this process, please contact me at [redacted]

Sincerely,

[redacted]

David F. Arons, JD
Senior Director of Public Policy

[1] http://www.lls.org/content/nationalcontent/pdf/ways/Milliman2014IndividualExchangePoliciesinFourStates_20140109.pdf

LEADING THE
FIGHT TO
END DUCHENNE

VIA ELECTRONIC DELIVERY

June 13, 2014

The Honorable Fred Upton
Chairman
Committee on Energy & Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight & Investigations
Committee on Energy & Commerce
2322A Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton, Representative DeGette and Members of the Committee:

Thank you for undertaking the 21st Century Cures Initiative. As both of you noted in introducing the initiative, such a comprehensive, thoughtful and bipartisan look at the multiple components of our research and development infrastructure – public and private – is urgently needed. We have achieved much as a nation, particularly in the decade-plus since we completed the mapping of the human genome. At the same time, a number of challenges on both the research and regulatory sides remain, hindering our ability to achieve what we all want most – effective and accessible therapies and treatments for the diseases of our day.

For 20 years, Parent Project Muscular Dystrophy (PPMD) has been leading the fight to end Duchenne Muscular Dystrophy. Duchenne is the most common fatal genetic disorder diagnosed in childhood, affecting about 1 in every 3,500 live male births, with about 20,000 new cases each year. The disease, which affects primarily boys, is caused by the lack of the protein dystrophin. This absence causes muscles to weaken and deteriorate. As patients with Duchenne age, muscle wasting leaves them unable to walk, to move their arms and, ultimately, to breathe, maintain heart function, and live.

Not a single disease-modifying therapy has been approved to treat Duchenne in the U.S. However, thanks to a decade or more of fairly robust public and private sector support for Duchenne research, about a dozen candidate therapies are in various stages of clinical evaluation today. PPMD and the entire Duchenne community are quite hopeful that the first-ever new drug application for Duchenne will be filed within the next year, with several more to follow in the next two to three years.

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LEADING THE FIGHT TO END DUCHENNE

Given the bleak landscape of existing therapies, for years PPMD has been actively leading efforts aimed at accelerating patient access to effective and safe therapies. PPMD has

- **Championed Legislation**: PPMD worked with Congress to enact the Muscular Dystrophy Community Assistance, Research & Education (MD-CARE) Act, bringing attention and focus to the muscular dystrophies by the federal government and ushering in a new era of scientific and therapeutic advancement for nine forms of muscular dystrophy. The bill was amended in 2008, and a second round of amendments is pending in Congress. We also help champion many of the patient-focused drug development provisions included within the FDA Safety & Innovation Act (FDASIA) and for their subsequent implementation and use by the FDA.
- **Supported Drug Development Research**: PPMD has funded over $45 million in research at major medical centers and biotechnology companies and has contributed directly to eight potential therapeutic projects in clinical testing for Duchenne.

- **Facilitated Trial Recruitment:** PPMD provided travel awards to clinical trial sites to increase the ability of trials to recruit on time and to ensure that trial participants were reimbursed promptly for expenses.

- **Educated patients and families:** PPMD informed the community about the research process, clinical trial involvement, and compounds under development and in trial.

- **Engaged and surveyed the population:** PPMD developed a patient self-report registry that is utilized by the large majority of clinical trial sponsors to explore feasibility, recruit for trials, and educate the community.

- **Documented Benefit/Risk Preferences:** PPMD conducted the first-ever scientific survey of Duchenne families to better understand their treatment preferences and perspectives on meaningful benefits and risk tolerance.

- **Facilitated Communications with Regulators:** PPMD convened the day-long FDA Public Policy Forum where more than a dozen senior FDA leaders engaged candidly with more than 100 Duchenne stakeholders on important therapy review and related issues.

Most recently, PPMD led the first-ever patient advocacy-led effort to develop a draft guidance document for industry developing therapies for Duchenne. The draft guidance, which is being submitted to the FDA this month, was developed using a rigorous methodology through a process that involved a comprehensive array of stakeholders including patients, clinicians, researchers and industry. PPMD believes this effort epitomizes what is possible via robust public-private partnerships, and we hope FDA will promptly review the draft so this important content can be further developed and finalized. We firmly believe that Duchenne can and should be used as a model for understanding community preferences and regulatory engagement for other rare disease communities.

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LEADING THE FIGHT TO END DUCHENNE

In the following pages, PPMD will provide comments to the specific questions you posed to the patient community in your May 16th white paper. We look forward to discussing this with you in greater detail and would be most pleased to participate in subsequent roundtables, briefings, hearings or other sessions as part of the 21st Century Cures Initiative.

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What is the state of discovery of cures and treatments for your disease? Are there cures and treatments now or on the horizon?

As noted above, the Duchenne community is fortunate to have a robust pipeline of clinical and preclinical candidates, but no approved therapy is yet available (Translarna™ was approved in Europe in May but won't be available to patients for another year). The sector has had its share of disappointing setbacks over the years. While we are most hopeful that long-awaited treatments for all patients with Duchenne muscular dystrophy are on the horizon, our enthusiasm is tempered by this history. We also recognize challenges presented by some therapeutics strategies that will only treat a sub-portion of the population of this already rare disease and the fact that most potential therapeutics will likely slow or stop progression of, rather than cure, the disease.

What programs or policies have you utilized to support and foster research, such as patient registries, public-private partnerships, and venture philanthropy?

Since its inception, PPMD has deployed a number of innovative strategies to advance Duchenne research. When we were formed in 1994, the public and private Duchenne landscape was practically non-existent. NIH funding for Duchenne was miniscule, and industry and venture capital was not present. PPMD recognized that, to achieve our goal of ending Duchenne, this simply had to change. Today, we have a vibrant and diversified multi-million dollar research portfolio supporting a number of innovative research projects at all stages. Our research investments vary greatly in size and range from relatively small sums of money that support planning or conferences to six-figure multi-year commitments.

In an innovative project to aggressively speed research, PPMD works with the National Institutes of Health (NIH) to fund projects relevant to Duchenne that just missed the payline or funding cutoff line. This program, called the "End Duchenne Grant Program," provides investigators with funding to address concerns of the NIH reviewers and ultimately increases their prospects of securing NIH upon a resubmission to NIH. Successes include a $220,000 End Duchenne grant by PPMD to Krista Vandenborne at the University of Florida to use magnetic resonance imaging to measure muscle wasting, which was later parlayed into a $7 million RO1 from NIH.

PPMD has used a "venture philanthropy" approach, by investing over $5 million in Duchenne therapeutic development at four biotechnology companies, resulting in one phase III study, two phase I/II studies and one additional study that will launch in late 2014. In addition, a pilot study funded by PPMD at an academic institution recently served as the basis for another phase III study conducted by a pharmaceutical company.

In another collaboration with industry, last fall Sarepta Therapeutics provided support for PPMD to help patients obtain cost-prohibitive genetic testing to better understand and more fully characterize the patient population. The program runs through our longstanding patient registry, DuchenneConnect.

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DuchenneConnect is a patient/caregiver report registry that began in 2007 with funding from the CDC. From 2011 to 2014 it was funded entirely by PPMD. The registry includes data on about 3,000 patients and is a community resource, offering educational materials, information about upcoming and recruiting trials, and access to a genetic counselor. Sponsors of clinical research use DuchenneConnect for feasibility planning, study recruitment, and communicating updates and results. Last year alone, the registry was used to recruit for a dozen clinical trials. Early in 2014, DuchenneConnect took an important step forward. The registry was chosen as a Patient-Powered Research Network under PCORI's PCORnet program, allowing improvements to the user experience, enhanced efforts to engage the community about research priorities, and act on those priorities through the PCORnet Network.

In July 2014, PPMD will host, in partnership with the National Heart Lung and Blood Institute (NHLBI), a two-day working group looking at evaluating "Contemporary Cardiac Issues in Duchenne Muscular Dystrophy." Typical survival in Duchenne is only into the third decade of life. Improvements in supportive and respiratory care have shifted the morbidity and mortality to cardiac complications in the muscular dystrophies. Heart failure is now one of the most common causes of death in patients with Duchenne.

How can Congress incentivize, coordinate, and accelerate basic research for diseases we know relatively little about?

First and foremost, Congress must continue to support a robust biomedical research enterprise at the NIH and ensure adequate funding is available to advance our understanding of diseases we know little about, conditions that often fall into the rare disease category. Congress can also support programs and initiatives that span multiple institutes or centers while ensuring that all of the research is appropriately coordinated. Duchenne research, which is funded by multiple institutes, is a great example of the reality of many conditions that touch a number of organ systems or categories and that require investigation from multiple angles. Continuing to publicly report estimated and final levels of funding allocated to each disease is helpful and ensures continued transparency. Congress should also look at some of the lessons learned elsewhere and apply them as appropriate to the biomedical research space. For example, the Defense Advanced Research Projects Agency or DARPA is widely regarded as an extremely effective entity for cracking high-risk but high-reward research questions. Developing more partnerships between NIH and DARPA, as well as other innovative approaches, may be warranted going forward.

How can we work together to better translate advances in science into safe and effective new therapies for patients?

We can better translate advances in science into safe and effective new therapies by identifying and addressing known barriers to translational research through the elimination or reform of inefficient processes and the provision of strategic incentives. For example, in clinical trials for Duchenne (and many other diseases), major barriers include:

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- Variability at trial sites due to lack of care standards or uneven care. PPMD has addressed this issue by supporting the development of "Care Considerations" through the Centers for Disease Control, and by developing a clinical care certification program for Duchenne clinics.

- Use of individual institutional review boards (IRBs) in multi-center trials that requires that every protocol change be approved by each site's IRB. PPMD is working to develop a network of trial-ready sites for Duchenne that makes use of a Central IRB for all studies.

- Natural history and trial data that is "siloed" in individual databases. PPMD is working to develop a central, de-identified data repository where these data sets can be combined and used to model faster and more efficient trial designs for Duchenne.

- For Duchenne and similar disorders that have a high disease burden and uncertain treatment benefits and risks, it is vital to explore treatment preferences with the patient and/or caregiver community as part of the translation process. For these types of disorders, safety may not have to be as well determined and patients/caregivers may accept higher risks and side effects in exchange for even moderate benefits. (See the Benefit/Risk item below.)

Additional barriers to therapy development that are applicable across all disease areas include the lack of uniform electronic medical records, under-resourced contracting offices at the universities that usually host clinical trial sites and a lack of harmonization between regulatory requirements of the Food and Drug Administration and the European Medicines Agency. Support from Congress through legislation that addresses these types of barriers can have an out-sized impact across many disease areas.

How do you coordinate your research and outreach with other patients?

Research

PPMD is proud of our longstanding history of collaboration with other partners, including other patient organizations that focus on other forms of muscular dystrophy as well as those focused on specific mutations of Duchenne. All of the projects that receive funding from PPMD are posted in our online database in a highly transparent manner. This data includes the total amount of the award.

This year, PPMD launched My Donor Portfolio to bring in other patient groups and stakeholders interested in partnering to fund research grants. This system allows partners to view peer-reviewed grants accepted by PPMD's scientific advisory committee and commit funds to those projects. PPMD also contributes data to the Health Research Alliance's gHRAsp database, which aggregates data from over 58 health funding organizations representing more than $1.2 billion

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in private funding. This data base allows our organization and others to identify emerging trends in research, potential project duplications, and cross-disease commonalities.

PPMD also uses an array of social media tools to communicate about potential collaborations on research initiatives and opportunities.

Outreach

Through an extensive outreach strategy, PPMD uses those same kinds of tools to reach patients around the globe. Through our patient registry, DuchenneConnect, patients who meet the inclusion criteria for trials are informed via email regarding the trial.

For 20 years, PPMD has hosted its Annual Connect Conference, which brings together all stakeholders in the Duchenne community, including families affected by Duchenne, drug developers, government agencies, other Duchenne-funding organizations and academic investigators. The conference serves to update all stakeholders on the state of the science and to promote collaborations within and across these groups.

In 2007, PPMD launched Duchenne FACES (Families Advocating Connecting Educating and Supporting). This program, piloted by CDC funding, created volunteer outreach groups around the country in order to create a national outreach network connected to PPMD's headquarters in Hackensack, New Jersey. These regional groups connect families with one another, serve as mentors for the newly diagnosed, hold educational seminars and meetings at no cost to families, and help educate local physicians and early childcare providers about Duchenne.

PPMD also participates in a number of umbrella organizations that coordinate policy and strategies across multiple diseases including the National Organization for Rare Disease (NORD), the Genetic Alliance, the Health Research Alliance and FasterCures.

How do you learn about new treatments and cures? How do you communicate with other patients regarding treatments and cures?

PPMD is fortunate to have 20 years of experience in the Duchenne research space. Our scientific advisors include most of the leaders in the field, nationally and internationally. Many of our advisors or grant recipients are the very same people achieving the breakthroughs that we hope will result in treatments and cures for Duchenne. We also have built, over two decades, very strong relationships with all of the biopharmaceutical entities working or considering working in the Duchenne space. These range from small upstart biotech companies to some of the world's largest pharmaceutical manufacturers. PPMD staff and/or advisors participate in nearly every Duchenne-related research gathering throughout the globe. We also convene the above-mentioned annual Connect Conference, which focuses on sharing the latest research and clinical information with our patient community. Based on this history and experience, PPMD is considered a valuable information source and partner by clinicians, researchers, and sponsors, who typically seek out our input and advice.

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PPMD has many robust mechanisms to communicate with patients and families. We have an extensive database of over 20,000 names that we communicate with regularly as well as the greatest reach via social media of any Duchenne-specific organization. In early 2014, PPMD reached 15,000 "likes" on Facebook and over 2,300 followers on Twitter. These sites – as well as our PPMD channel on YouTube and our presence on Instagram, LinkedIn and Flickr – allow families to find us via the social media application they are most comfortable with and stay abreast of critical Duchenne news and information. The DuchenneConnect registry communicates independently with registrants through a newsletter, emails targeted at relevant communities, the website, and webinars.

What can we learn from your experiences with clinical trials and the drug development process?

The DuchenneConnect registry provides education for and access to a group of patients and caregivers who have opted into providing information for research use. This allows more targeted messaging and reduces concerns about sending patients and families unwanted information or requests for participation. In addition, sponsors receive anonymous feasibility information about – and can deliver their recruitment materials to – a community that wants to participate in such projects.

Many families have shared their experiences in clinical trials (including their decision making, perception of benefits and satisfaction levels) with PPMD through a study funded by the NINDS. Understanding the decision making process and clinical trial experiences allows PPMD to advocate for regulatory changes, protocol flexibility and communication approaches that meet needs identified by participants, to improve the experience of families to come.

We have also learned through focus groups with Duchenne trial sponsors what specific challenges they see in conducting trials in this space, including the need to aggregate trial data in a central repository, promote the use of central rather than individual institutional review boards and provide better resources and training to trial sites.

What is the role of government in your work, including any barriers to achieving your goals and advancing breakthroughs?

Government plays an indispensable role and must be an active member of the public-private partnership. As noted earlier, before the enactment of the MD-CARE Act in 2001, public and private research funding for Duchenne was practically non-existent, and the therapy pipeline was barren. Today, NIH commits about $35 million annually to Duchenne research. While significant, it is a small fraction of the estimated $4 billion committed worldwide by public and private sources. While government investment typically won't be as great as industry, government investment sends an important message of interest and commitment, a message that often is needed to attract and retain industry engagement. Were government funding for

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Duchenne research to be sharply reduced or disappear altogether, the negative ramifications would be profound. In addition to funding research, government plays an important role as a convener. Thanks to the leadership of the government, we have a comprehensive Action Plan for the Muscular Dystrophies that is supported by multiple departments and agencies. Government also plays an important role in accountability and oversight to make sure all necessary entities are at the table and doing what they should be doing.

With regard to barriers, the most significant at this time are in the areas of FDA review of products. While FDA has multiple tools at its disposal, and was recently provided by Congress with even more tools, we share the concerns of many regarding their use, particularly in the spaces outside of cancer and HIV/AIDS. Challenges would include a dearth of clear guidance to industry in planning and implementing trials, particularly in small rare disease populations; a lack of flexibility around what is required to validate a surrogate endpoint in rare disease; and a benefit/risk paradigm that that does not put enough weight on the risk of inaction. Such skewing is particularly troubling given a disease like Duchenne that lacks any disease-modifying treatments and is always fatal. It has become clear to us that these challenges have at their root an ingrained culture at the FDA that simply does not account for the realities of a rare, progressive pediatric disease. Another challenge is significant under-resourcing of the agency.

How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?

While the evaluation of a product's potential benefits and risks is similar regardless of indication, it is imperative for Duchenne disease stakeholders that the FDA develops a benefit/risk paradigm that recognizes greater thresholds for uncertainty and willingness to take risk, particularly when the only alternative would be decline and, ultimately, death. For disorders that have a high disease burden, uncertain treatment benefits and risks and harms that result from not treating, exploration of treatment preferences is vital. In these cases, FDA's typical benefit/risk judgments, made by individuals who do not have direct disease experience, falls short.

We are concerned about the use of patient/family testimony as the primary way that the FDA learns about preferences, in that it is not systematic or quantitative but rather anecdotal in nature. Although family stories are compelling, those who testify may not represent the views of many other patients/families, and these approaches greatly limit the voice of families who cannot travel to FDA meetings. Recognizing that FDA's decision-making process is primarily data-driven, the use of systematic, quantitative documentation of patient preferences should provide a powerful source of information to complement the anecdotal testimony.

Last year, PPMD conducted the first-ever rigorous scientific survey of treatment preferences, meaningful benefits, and risk tolerance of 119 Duchenne parents or guardians. The study was lead by PPMD using a community-engaged approach, in partnership with an expert in stated-preference methods. Data from the study illustrates a relatively high level of risk tolerance if the potential benefit is slowing or stopping the progression of muscle weakness. The survey data

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has been presented to FDA leadership several times, beginning in meetings one year ago and continuing through spring of 2014. PPMD developed a model process for disease communities, and continues to work with the agency to apply this approach to other disease indications and most importantly, in the FDA's benefit/risk assessment.

The first article from PPMD's treatment preferences study has been published: Peay HL, Hollin I, Fischer R, Bridges JFB. A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. *Clinical Therapeutics* 2014;36:624–637.

To keep the family voice front-and-center, PPMD also engaged in a community-wide effort to collect and compile family stories. This "Share Your Story" has resulted in the collection of more than 175 family stories. Most families agree to allow the FDA to read their stories, and this collection will be presented to the FDA in summer 2014.

What is the role of public and private funding in the research and development of cures and treatments?

As noted above, public and private funding are both incredibly important. Public funding sends an important message and helps support much of the early-stage basic or laboratory research that is typically not funded by industry, and that is often too expensive for patient advocacy groups and philanthropists to fund alone. Private funding is equally important. While government funding may help yield early breakthroughs, it is industry and venture capital that will be needed to take those promising discoveries into candidate treatments. This would include the high costs associated with clinical testing, particularly clinical trials. Such costs are even greater in the rare disease context, where enrolling enough patients into a study is often a key hurdle.

While privately-funded initiatives can often be implemented more quickly and take more risks, public funding can be used to stabilize or expand to other disease areas once private initiatives have proven successful. Public funding can also provide important incentives across broad areas for improvements or change that can be difficult to accomplish with private funds alone.

In summary, both the public and private sectors play invaluable roles in supporting Duchenne research and moving us closer to the development of treatments and cures. When these efforts are coordinated so that each plays to its strengths, greater progress is made.

Are there success stories the committee can highlight and best practices we can leverage in other areas?

As a result of MD-CARE Act, the Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities (NCBDDD) supported the development of a set of priorities that would standardize the healthcare and improve the health outcomes for

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individuals living with Duchenne. The purpose of these recommendations "is to provide a framework for recognizing the primary manifestations and possible complications of the condition and planning optimal treatment across different specialties with a coordinated multidisciplinary team." These comprehensive guidelines, known as the Care Considerations, were published in *Lancet Neurology* in 2009 & 2010.

Given the historically bleak landscape for care, PPMD has been active for years, striving to reduce gaps and to address discrepancies in standardizing and improving Duchenne care. The organization has also worked to increase patient access to sites offering comprehensive care across the United States. In 2012, PPMD held the first Transforming Duchenne Care meeting. This meeting brought together 53 key community stakeholders, including medical providers, hospital administration, industry, advocacy and parents, to address these issues of discrepancies in care across the U.S. The result of this meeting was the Transforming Duchenne Care Initiative (TDCI).

The TDCI is divided into four phases: transparency of clinical services, transparency of clinical care, PPMD's Certified Duchenne Care Center Program and the development of a network of Certified Duchenne Care Centers. The certification of clinics is intended to ensure clinics maintain the highest standards of comprehensive care and services, rapidly apply new evidence-based knowledge and comply with standards for care that were established by the CDC Care Considerations. With this new program, PPMD will further transform Duchenne care.

PPMD has engaged in a range of successful efforts to understand the priorities and preferences of our community. This understanding has allowed us to advocate more effectively for the needs of a wide range of families, to researchers, sponsors, regulators, and Congress. Foundations should engage in meaningful efforts to move beyond testimony and anecdote in their assessments of their communities.

How have you worked with other patients to support one another?

As noted above, PPMD is fortunate to have a long history of collaboration and partnership, including with other Duchenne-specific organizations as well as groups focused on Muscular Dystrophy and related conditions more broadly. PPMD connects the patient community through a social networking stand-alone website, community.parentprojectmd.org, where patients and families can share stories, resources, and find other families in their area of the country and the world. In rare disease, social networks connect patients and families faster than ever before. Where families once felt isolated and alone, they now have an online network of people who are going through the same obstacles to daily living and dealing with the same issues regarding care and management.

What is the financial burden of your disease? How would better treatments and cures help save money for your family and the federal government?

The financial burden of Duchenne is significant. A recent study (Larkindale et al. "Cost of Illness for Neuromuscular Diseases in the United States" *Muscle and Nerve*, 2014 Mar;49(3):431-8) has

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calculated the annual cost of care for Duchenne in the United States at $800 million, but with the caveat that actual costs may be 34 to72 percent higher, due to technical challenges in the measurements.

Due largely to efforts to standardize diagnosis and care, most patients are diagnosed by age 5. Immediately upon diagnosis, patients should begin treatment regimens that include visits every 6-12 month to a variety of medical providers, including at the very least, neurology, cardiology, physical medicine and rehabilitation, pulmonary, genetics, nutrition, physical therapy, orthotics, and social work. In addition to the physical delays, most children with Duchenne are also challenged by cognitive delays, psychosocial issues, and behavioral issues, which require treatment and management. Currently, corticosteroids are the only proven treatment for this diagnosis. As children age, the disease progression and chronic corticosteroid treatment result in additional medical issues. These may include vertical growth and pubertal delay, gastrointestinal and genitourinary issues, osteopenia/osteoporosis, pulmonary compromise and heart failure.

Currently, access to centers that are able to offer standardized comprehensive care often means long-distance travel, at least annually for many families. Not only are the costs of travel, room and board incurred, but lost income from days of work missed and the cost of care for children left at home compound this expense. As patients decline and lose muscle function, they require assistive technologies, including power wheelchairs that cost an average of $20,000-30,000. These chairs, of course, do not fit into a regular van, and wheelchair accessible vans cost upward of $60,000. In addition to a wheelchair, many patients require pulmonary assistive devices (cough assist, Bi-PAP machines), which are not always covered by health insurance plans.

Many patients also require personal attendants able to assist them at school or work. While some states cover partial cost of this service, many states do not, leaving parents with the choice of limiting their child's independence or scraping to pay out of pocket for assistance. Home renovations needed to accommodate the needs of a child with progressive deficiencies and wheelchair mobility can be exorbitant. While most Duchenne families qualify for Medicaid because of the costs associated with the care, many of these costs are not covered at 100 percent and many are not covered at all. Needless to say, many parents deplete their savings and retirement funds attempting to meet the needs of their child.

How can Congress help?

Pass the MDCA Amendments

The MD-CARE Act is a shining legislative success, exemplifying what can be achieved through genuine public-private partnerships to transform the biomedical research and drug discovery landscape. So many critical programs were made possible because of the bill and follow on reauthorization. But while much has been accomplished, more remains undone and in need of federal support to continue driving and leveraging non-federal funding. The current update to the legislation (HR 594/S315) is awaiting Committee action. We urge the Energy and Commerce Committee to take action soon so we can enact the legislation into law before year's end.

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Increase funding at the NIH

Though an obvious suggestion and one we imagine all patient groups will encourage, the commitment by the federal government in the NIH over the past 13 years made a tremendous difference in changing the landscape for Duchenne. Because of consistent support and focus by the federal government, we now have a drug pipeline full of promise. The commitment spurred a public-private partnership that helped to build a road to potential therapies. The federal investment impacted outcome measures, data collection, basic science, translational research and care considerations. Many of the pieces that were missing in our puzzle to develop drugs for Duchenne were eventually found through the public-private partnership that continues to strengthen over time.

FDA reforms: Expand Patient Focused Drug Development (PFDD)

Congress should build upon the FDASIA provisions and support and encourage community-centered approaches for drug development. Rare disease communities hold the keys to understanding the full breadth of knowledge for their disease. Educating the FDA about the unmet medical need, patient benefit/risk considerations, and what outcome measures are most meaningful can only occur through direct engagement with the patients and families who live these diseases on a daily basis. Congress made major advancements in this direction with the passage of FDASIA and the provision on PFDD. Congress should engage with patient groups on novel efforts to further the agency's understanding about disease. Duchenne is an ideal model in this respect and PPMD's benefit/risk initiative and leadership of the development of draft guidance on Duchenne are both novel and unprecedented examples of patient focused drug development, leadership that can be translated more broadly. In many cases the most forward looking and innovative ideas come from the communities of rare disease patients and families--advocates who don't have time to spare. The most efficient way to unlock therapies for rare conditions is to encourage the development of community centered approaches to drug development.

Pilot the use of adaptive approval for serious and life-threatening disorders

Using existing authority under current law, the FDA should pilot the use of adaptive approval for serious and life-threatening disorders with significant unmet medical need.

In its 2012 report on propelling innovation in drug discovery, the President's Council of Advisors on Science and Technology or PCAST recommended that the FDA should further promote access to therapies for serious and life-threatening illnesses where there is unmet medical need by piloting the use of adaptive, i.e., provisional, approval under its existing authority. PPMD endorses this recommendation and further urges the FDA to prioritize the use of adaptive approval under such a pilot program to evaluate drugs for rare disorders, including Duchenne, that meet the criteria of "serious or life-threatening." As has been established, the FDA and Congress have taken steps to reinforce the need for flexibility in evaluating drugs to treat serious and life- threatening disorders, and the passage of FDASIA has further underlined the need to apply this flexibility to the evaluation of rare disorders.

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The FDA can grant approval for drugs while requiring that post-marketing trials be conducted to provide additional evidence of efficacy and safety (see 21 CFR §312.85). While the Agency has infrequently revoked approvals on the basis of the failure of applicants receiving accelerated approval to conduct post-marketing studies, it could capitalize on its ability to require post-marketing studies to facilitate a pilot of adaptive approval. This would allow for the safety and efficacy of drugs to be subjected to continuing evaluation, while providing patients in need with earlier access to potentially life-saving drugs, subject to the proviso that drugs demonstrating insufficient or negative results would have marketing approval revoked.

Given the number of promising investigational compounds under development for the treatment of Duchenne and the ongoing challenges in designing and conducting traditional clinical trials for these treatments, most notably a small, primarily pediatric patient population characterized by high clinical variability, PPMD recommends that FDA move quickly to establish a pilot program to evaluate treatments for Duchenne using adaptive approval. PPMD and the advocacy community stand ready to work with FDA and other stakeholders to undertake a process, as recommended by PCAST, "to help define potential evidentiary standards, protection of patient safety and rights, and mechanisms to ensure timely post marketing clinical studies and withdrawl of drugs".

Give greater weight to Post Hoc Analysis for potential rare disease New Drug Applications

While post-hoc analysis are generally not accepted by the FDA as supporting an NDA, we would ask the FDA to use flexibility in the case of rare diseases. Historically, there has been a real distinction between consideration of pre-specified analyses versus post-hoc statistical analyses. It is inherent in any orphan or ultra orphan disease, including Duchenne, that as collection of natural history data continues to evolve, novel endpoints will emerge (particularly in the non-ambulant disease of Duchenne) and knowledge about "established" endpoints will also evolve. One must view the data and the evidence moving forward through that lens, appreciating that this will naturally lead to post-hoc statistical analysis based upon emerging concepts of natural history. Regulatory agencies should exhibit some flexibility with regard to post-hoc analyses; otherwise, the field will be littered with 'failed' drugs that have not actually failed, but were merely tested in the wrong population (i.e., the wrong age group or stage of disease), or using the wrong endpoints, because of the limited knowledge about the disease.

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Conclusion

Thank you, again, for initiating this critically important undertaking. PPMD applauds you for your leadership and looks forward to working with you and your staff to move this initiative forward. We hope you have found our responses to be informative and helpful. We strongly believe that the comprehensive undertaking we have been leading to accelerate access to Duchenne therapies while improving care and quality of life can be a role model for novel, innovative, and public-private partnerships. While our work has been focused in Duchenne, much of this can serve as a replicable blueprint for other conditions, particularly rare and ultra-rare disorders. We would be most pleased to participate in any meetings, briefings, roundtables or hearings on 21st Century Cures, and we invite you to reach out with any follow-up questions or requests for information.

Sincerely,

[redacted]

Pat Furlong
Founding President & CEO
Parent Project Muscular Dystrophy

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SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

June 5, 2014

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
2368 Rayburn House Office Building
Washington, DC 20515

RE: 21st Century Cures Initiative

Chairman Upton and Ranking Member DeGette:

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) appreciates the opportunity to submit comments on the 21st Century Cures Initiative. SNMMI supports the aim of the initiative, to accelerate the pace of cures and medical breakthroughs in the United States

SNMMI's more than 18,000 members set the standard for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals, meetings, and leading advocacy on key issues that affect molecular imaging and therapy research and practice.

In response to your timely white paper, entitled *21st Century Cures: A Call to Action*, we propose accelerating the availability of personalized and effective diagnostic imaging tools to help develop treatments and cures for the twenty-first century and beyond. We believe one way this could be achieved is for the U.S. Food and Drug Administration (FDA) to establish simplified and/or alternative pathways for the approval, for commercial marketing, of radiopharmaceuticals for diagnostic applications and radiotracers for biomarker applications (hereafter referred to as "imaging biomarkers").

Diagnostic radiopharmaceuticals and imaging biomarkers are radioactive drugs administered to patients to produce images ("scans") of the body, predominantly images useful to disease detection and assessment of important body functions. Once the radioactive drug is administered to a patient, highly sensitive nuclear medicine scanning machines detect the radioactivity to produce an image, even though very small quantities of the radioactive drug were administered. Hence, clinically useful images are obtained even though the actual quantity of drug administered to the patient is typically very small.

Currently, the FDA regulates diagnostic radiopharmaceuticals and imaging biomarkers in much the same manner that therapeutic drugs are regulated, applying very similar manufacturing, non-clinical testing and clinical trial expectations despite major differences between the drugs. For example, a typical diagnostic radiopharmaceutical or imaging biomarker contains a quantity of radioactive drug that is far below the level even remotely associated with a potential for an adverse drug effect. If the FDA continues to regulate diagnostic radiopharmaceuticals and imaging biomarkers in the current manner, we are at risk of not only depriving patients of potentially critical diagnostic information, but also failing to take advantage of the unique role these drugs may have in accelerating therapeutic drug development. This availability gap will likely continue to widen unless changes are made to the FDA's

approval process for these agents. In addition, the FDA's current regulatory approach contributes substantially to the high cost of bringing these valuable tools to market resulting in the withdrawal of business enterprises from the development and commercialization of diagnostic radiopharmaceuticals and imaging biomarkers, further limiting the availability of potentially lifesaving diagnostic agents and their promising future in the area of biomarker applications.

We believe that dedicated and appropriate FDA approval pathways for these radioactive drugs would result in increased and expanded clinical access, thereby, helping to ensure the continued role of the United States as a world leader in development of medical diagnostics and therapies.

Unique Safety Features of Diagnostic Radiopharmaceuticals and Imaging Biomarkers

Unlike traditional (i.e., therapeutic) drug products, the use of diagnostic radiopharmaceuticals and imaging biomarkers in medicine is not based upon their pharmacologic effects within the body but, rather, on the ability to safely image and quantify their pharmacokinetic properties. Such properties are largely defined by the molecular, biological or physical (including anatomical) process (i.e., the biomarker) that is being targeted by the radioactive drug. The actual amount of "biologically active" drug component of these radioactive drugs is typically in the nanogram or microgram range, well below the level that has a potential for an adverse effect. Thus, as would be anticipated, side effects or adverse reactions (i.e., of any severity) are very rarely observed with these radioactive drugs, both in clinical use and research studies. An additional risk consideration for these radioactive agents is the radiation dose that they deliver to the patient. Fortunately, the radioactive drugs being developed for biomarker and diagnostic applications incorporate radionuclides with very short radioactive half-lives and deliver dosages which are recognized as being "generally safe" by the FDA. Another safety consideration is related to the fact that, unlike traditional (therapeutic) drugs, radioactive agents for biomarker and diagnostic applications are typically administered a very limited number of times to a given patient over a relatively extended time period. Also radioactive agents for human use are currently required to be manufactured and their quality must be assured in conformance with the FDA's current Good Manufacturing Practice regulations at 21 CFR Parts 210, 211, and 212.

We are concerned that the FDA currently does not sufficiently recognize the unique safety considerations for these radioactive drugs in assessing the overall benefit-to-risk consideration needed to support approval and commercial marketing. Given a profoundly low risk for harm, a suitable benefit-to-risk ratio for these radioactive drugs can be maintained with a commensurate reduction in the extent of diagnostic benefit (i.e., effectiveness) that must be demonstrated with their use.

The FDA's Current Requirements for the Demonstration of the Benefit of Diagnostic Radiopharmaceuticals and Imaging Biomarkers are Excessive

In recognition of the unique safety considerations for diagnostic radiopharmaceuticals and imaging biomarkers, we believe the FDA's current requirements for the demonstration of the diagnostic benefit (i.e., effectiveness) of these agents are often excessive and inconsistent with how these drugs would be used in clinical practice. As stated previously, the use of radioactive tracers and diagnostic radiopharmaceuticals in medicine is based on their ability to image and measure molecular, biological, or physical characteristics associated with underlying physiological or pathophysiological processes; i.e., their ability to image biomarkers. Nonetheless, the FDA's current approach for the approval of such radioactive agents focuses mainly on the ability of these agents to provide, often independent of other

patient information, an accurate diagnosis of a certain disease or condition. This approach does not take into account the fact that physicians routinely rely on multiple sets of information in making a patient care decision. Thus, an expectation that the benefit (i.e., efficacy) of a radioactive agent must be based on its ability to independently establish an accurate diagnosis is typically inappropriate. Moreover, this current approach fails to recognize the potential benefit that may accrue from the use of an imaging biomarker as one of the multiple diagnostic information components necessary to make a patient care decision. We believe the FDA's approval process for these drugs needs to be amended so as to recognize and be commensurate with the drugs' unique benefit-to-risk considerations.

The FDA Should Develop an Alternate Approval Pathway for Imaging Biomarkers for the Use in the Drug Development Process

Over the past several years, the FDA has promoted, as one of its Critical Path Initiatives, the potential of biomarkers to accelerate the development of traditional, therapeutic drug products and to direct the delivery of personalized medicine. Yet, despite the obvious alignment between the attributes of radiotracers for biomarker applications and the respective goals of the FDA, only a few radiopharmaceuticals have been approved for commercial marketing over recent years.

In order for the agency to grant approval to commercially market a drug product, there must be sufficient data to demonstrate that the drug product is both safe and effective for its intended clinical use, which for radiotracers is typically their ability to safely and accurately diagnose or aid in the management of a disease or condition, delineate anatomy or characterize a physiological-biological function. However, this current process fails to fully recognize that the *in vivo* use of a radiotracer for the specific purpose of identifying and measuring a biomarker may not, in itself, provide diagnostic or definitive clinical information. Rather, imaging biomarker information may help a clinician understand and characterize a patient's disease or condition when combined with other clinical information. Further, even in the absence of providing independent diagnostic information, imaging biomarkers may importantly accelerate the drug development process because they may provide the earliest evidence of therapeutic drug effects. In summary, it is important to recognize that imaging biomarkers have clinical utility and commercial value even though they may not independently diagnose a disease or definitively affect patient outcomes.

In its recent report, entitled *Paving the Way for Personalized Medicine*, the FDA emphasizes that the use of biomarkers for drug development and the delivery of personalized medicine involves a relatively complicated multi-part, sequential process. At the end of this process, FDA approves the imaging biomarker for clinical use and commercial marketing only upon the agency's determination that it meets the requirements for a companion diagnostic test (i.e., the final step in the biomarker development process that combines use of the biomarker with the use of a new therapeutic drug) or meets the evidentiary expectations for a diagnostic imaging drug product. As a result, the imaging biomarker's success is tied to the success of the new therapeutic drug and/or the development of all the data typically necessary to support approval of a diagnostic imaging drug product. In light of these cumbersome and complex processes, we believe the continued development of imaging biomarkers would benefit greatly from an amended FDA-approval process that would permit their approval for commercial marketing for use earlier in the biomarker development process. Moreover, approval to commercially market an imaging biomarker should be based only on data that demonstrate the safety and the analytical validity of the radiotracer to identify and measure or characterize a biologically

important process or molecule. Compared to the current FDA pathway for approval of a radiopharmaceutical for a diagnostic application, the approval of an imaging biomarker should not require clinical data to demonstrate that the drug provides clinically useful information independent of other diagnostic information.

In conclusion:
In the absence of amended FDA approaches for the approval of diagnostic radiopharmaceuticals and imaging biomarkers, we anticipate markedly diminished development of these important drugs, a problem that will importantly limit advances in medicine as well as patient access to the drugs. The recent withdrawal of major companies from further development of radiotracers for Positron Emission Tomography is evidence of this concern. Adoption of the amended FDA-approval approaches outlined above would facilitate the approval of, and increase physician and patient access to new diagnostic radiopharmaceuticals at a lower cost. It would also permit the commercial marketing of imaging biomarkers based on less data requirements and associated development costs, and would expand the access to FDA-approved, validated radiotracer/biomarker packages by multiple entities that are involved in the qualification of the respective biomarker for various diseases or conditions and/or for use in accelerating their drug development efforts.

In summary, SNMMI wholly supports the aim of the 21st Century Cures Initiative, to enact changes in the current regulatory and delivery system to ensure the continued advancement of medical science and clinical care in the United States. As such, the Society respectfully requests that the Committee examine the current FDA regulatory process used to approve diagnostic radiopharmaceuticals and imaging biomarkers. Modifying the current pathway will help spur continued investments and innovations in the healthcare sector that may translate into treatments and cures for patients worldwide.

SNMMI is ready to discuss any of its comments or meet with your offices on the above issues. In this regard, please contact Susan Bunning, Vice President, Government Affairs, by email at [redacted]

Sincerely,

[redacted]

Gary L. Dillehay, MD, FACNM, FACR
President

ALZHEIMER'S FOUNDATION OF AMERICA

Our mission is "to provide optimal care and services to individuals confronting dementia, and to their caregivers and families—through member organizations dedicated to improving quality of life."

June 13, 2014

The Honorable Fred Upton
The Honorable Diana DeGette
House Committee on Energy and Commerce
US House of Representatives
Washington, DC 20515

Via Electronic Submission

Dear Chairman Upton and Representative DeGette:

On behalf of the Alzheimer's Foundation of America (AFA), a national nonprofit that unites more than 1,700 member organizations nationwide with the goal of providing optimal care and services to individuals confronting dementia, and to their caregivers and families, I am writing to comment on the 21st Century Cures Initiative and how Congress can facilitate biomedical research and therapeutic advances in finding a cure or effective treatment for Alzheimer's disease.

What Is Alzheimer's Disease?

Alzheimer's disease is not part of the normal aging process. It is a fatal, irreversible, progressive brain disorder that destroys memory and intellectual function. Common symptoms include memory loss, confusion, spatial disorientation, lack of judgment, and inability to communicate.[1] Over a period of years, the disease leads to the complete loss of cognitive function, a long period of dependency and, ultimately, death.

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[1] National Institute on Aging, Alzheimer's Disease Fact Sheet, (www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet).

Alzheimer's disease is the sixth leading cause of death in the United States and is the only condition with no cure or treatment to reverse or slow its progression.[2] A recent study indicates that the death rate is for persons living with Alzheimer's disease are underreported and that as many as 500,000 Americans die of Alzheimer's disease a year, potentially ranking it as the third leading cause of death.[3] It is also the only growth category in the top ten causes of death in the U.S., as recorded by the Centers for Disease Control and Prevention, and the *only condition in the top ten causes of death with no cure or treatment to reverse or slow its progression.*

As our nation faces the unprecedented public health crisis posed by Alzheimer's disease, AFA believes it is critical to advance efforts for drug development, and to do so in a fashion that accelerates the process while ensuring participant safety and drug efficacy. In 2013, the Food and Drug Administration (FDA) issued draft *Guidance for Industry Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease* which recognizes the need to focus on individuals earlier in the disease process.

AFA agrees that focusing on early stages of Alzheimer's disease will help stimulate drug development while having the greater impact on this group of people. Both the legislative and regulatory framework must, therefore, address the need for early and accurate diagnosis and the challenges in identifying individuals with early stages of Alzheimer's disease while accurately measuring appropriate outcomes, fostering innovation, facilitating international efforts, eliminating regulatory barriers, promoting clinical trial outreach and spurring public/private partnerships.

Early Detection and Memory Screening

AFA has long supported efforts to increase awareness of the importance and benefits of early detection of Alzheimer's disease and related dementias. Early identification of at-risk individuals provides multiple benefits to the person with Alzheimer's disease, the caregiver, the family and society. For the affected individual, identification of early-stage dementia allows a better understanding of and dialogue about the disease, early and appropriate use of beneficial treatments and social and behavioral interventions, planning for the future, and utilization of support services for themselves and their families.

Additionally, accurate and timely diagnosis can provide greater opportunities for people with Alzheimer's disease to participate in clinical trials. New drug therapies currently being tested

[2] Centers for Disease Control, September is World Alzheimer's Month (www.cdc.gov/features/worldalzheimersday/).
[3] James, Bryan Ph. D., et. al., Contribution of Alzheimer disease to mortality in the United States, *Neurology*, March 5, 2014 (www.neurology.org/content/early/2014/03/05/WNL.0000000000000240.short).

focus on stopping progression in the early stages of the disease, requiring trial participants to have low to mild cognitive impairment. Greater participation in clinical trials is essential in order to accelerate drug development.

AFA **urges Congress to advance policy that promotes cognitive assessment exams and increase awareness for the need to get a "check up from the neck up."** Other federal health programs need to join Medicare which includes a cognitive assessment as part of its annual wellness exam.

Establishment of Biomarkers

Development of a valid biomarker – such as a protein in blood or spinal fluid – is needed for an effective treatment by helping doctors measure a person's risk or track progression of the disease. AFA can appreciate the difficulty in developing meaningful diagnostic criteria for preclinical Alzheimer's disease. It seems reasonable to use genetic, clinical and validated biomarker based criteria for enriching trial populations with people in the early stages of Alzheimer's disease as well as with minority populations and those who may be genetically predisposed to the disease. AFA **urges Congress to adopt policies and provide necessary resources that will lead to development of valid and universally recognized biomarkers for Alzheimer's disease.**

Expand Medicare Coverage of Amyloid PET Imaging

New classes of PET tracers offer the opportunity to identify beta-amyloid plaques in the brain. The proteins *tau* and beta-amyloid are commonly found in people with Alzheimer's disease. Tracking accumulation of amyloid plaque in persons with Alzheimer's disease can lead to earl and accurate diagnosis of the disease.

Yet, in September 2013, the Centers for Medicare and Medicaid Services (CMS) issued a coverage determination which limits reimbursement for amyloid PET imaging to only those beneficiaries who are participating in Medicare approved clinical trials. AFA **urges Congress to work with CMS to review this overly restrictive policy.**

Compressing Regulatory Pathways to Market for Promising Therapies

Beneficial and promising drug therapies that will treat Alzheimer's disease or effectively slow its progression need to quickly come to market. To this end, AFA has endorsed legislation that calls for a partnership between HHS and non-governmental and non-profit venture entities with proven track records and expertise in developing and bringing therapies to market. Funds would be directed to goal-oriented and milestone-driven research initiatives; and the FDA would streamline the review process of therapies developed through the program to cut the

length and cost of the pipeline. AFA **urges Congress should explore such models and other innovative ways to eliminate unnecessary regulatory barriers that keep promising drugs from market.**

Support International Research Cooperation

Efforts are underway internationally to increase and coordinate funding for Alzheimer's disease research. A communique issued at last year's G-8 summit, committed G-8 nations (including the US) to developing a coordinated, world-wide effort to identify a cure or disease modifying therapy for Alzheimer's disease by 2025. Reps. Chris Smith (R-NJ) and Chaka Fattah (D-PA) have introduced a resolution in the House of Representatives, H. Res. 489, calling on Congress to facilitate and promote a robust response to the looming global crisis of Alzheimer's disease and other dementias and to create a global action plan and fund to fight the growing international dementia crisis. AFA **urges Congress to pass this resolution and commit to work more closely with international partners to share clinical research, data and resources.**

Clinical Trial Outreach

For Alzheimer's disease, one of the biggest obstacles to discovering a new treatment or prevention strategy is finding volunteers for studies to allow research to progress at the pace needed to develop more effective treatments. Education and outreach is especially needed in minority communities where persons are more at risk but barriers to recruitment are high. New outreach methods and awareness campaigns are needed to address this need for clinical volunteers across all demographics.

To help facilitate this outreach, AFA **urges Congress to**:

- **Establish large-scale patient registries** to facilitate faster and less expensive clinical trial recruitment.
- Call on public and private sectors to work together to **address the unique circumstances of individuals with Alzheimer's disease and their ability to provide informed consent** for clinical trial participation.
- Encourage all new and ongoing federally-funded and industry-sponsored Alzheimer's disease clinical trials to **use the same Alzheimer's disease data standards developed by the Clinical Data Interchange Standards Consortium (CDISC) in order to facilitate data sharing** and review by the FDA.

Public/Private Partnership

Scarce resources call for innovative solutions, through a collaboration of stakeholders, in how to best maximize research dollars and share data. The Accelerating Medicines Partnership (AMP) is a new venture between the National Institutes of Health (NIH), pharmaceutical companies and several non-profit organizations to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets of disease. The ultimate goal is to increase the number of new diagnostics and therapies for patients and reduce the time and cost of getting them to market. AFA **urges Congress to work with NIH to foster innovative public/private partnerships that can share both the risks and rewards of drug development.**

AFA appreciates and supports efforts of the House Energy and Commerce Committee to take comprehensive look at what steps Congress and other policy makers can take to accelerate the pace of cures in the United States. We are grateful for the opportunity to make comments and hope to continue working with the Committee to promote legislative and regulatory policies that fosters drug development in the Alzheimer's disease space. Feel free to contact me or Eric Sokol, AFA's vice president of public policy, at [redacted] if you have questions or need further information.

Sincerely,

[redacted]

Charles Fuschillo, Jr.

CEO

21st Century Cures: A Call to Action

Statement of the Association of Clinical Research Organizations

June 13, 2014

Summary of Recommendations for Congressional Action

In the statement to follow, ACRO identifies and offers recommendations for Congressional action across several broad topics:

I. Ensuring that the United States Remains Globally Competitive in Clinical Research

- Reduce the silo-ing of government, private sector and academic research initiatives. Specifically, **Congress should direct that the National Center for Advancing Translational Sciences (NCATS) of the NIH and the Patient Centered Outcomes Research Institute (PCORI) actively engage private-sector resources and expertise**, including the member companies of ACRO, in areas such as the development of data and research networks, project management, data management, trial design and feasibility, patient recruitment and the like.

- **Make the R&D tax credit permanent, simplify it, and extend a portion of the benefits currently not utilized to incentivize the conduct of clinical trials in the US**.

II. Unlocking EHRs and Other Big Data Sources

- **Congress should encourage inclusion of new EHR (electronic health record) functionalities** that will facilitate clinical and data-driven research **as part of the ONC/CMS Meaningful Use Phase 3 requirements**, including connectivity between clinicaltrials.gov and EHR systems to facilitate clinical trial recruitment.

- **Congress should amend HIPAA to define data research as part of health care operations at 45 CFR 164.506** in order to allow the use of protected health information for non-interventional studies.

III. Driving Innovation at the FDA

- **Engage the GAO or other 3rd party to review and prepare a report answering questions such as:** Is the FDA, an agency with scarce resources, receiving an adequate return on its investment in the Clinical Trials Transformation Initiative (CTTI) and similar public-private collaborations intended to produce "transformational" outcomes? Should the agency consider reallocating these funds toward additional investment in regulatory science or an increase in review staff?

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ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

- **Direct that the FDA appoint a Chief Innovation Officer** who shall be responsible for overseeing the Critical Path Initiative and will have the authority to agree to and enforce new, innovative approaches to drug development.

Background

The Association of Clinical Research Organizations (ACRO) represents the world's leading global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 100,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. CRO industry revenue is expected to reach $23.6 billion for 2014, representing well over one-third of *development* spending.

Each year, ACRO member companies conduct more than 11,000 clinical trials involving nearly two million research participants in 115 countries. On average, each of our member companies works with more than 500 research sponsors annually, and we have a broad and unique understanding of the roles, responsibilities and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards, clinical trial participants and ancillary providers of all types – that are part of the research enterprise.

As the Energy and Commerce Committee is well aware, the current methodology for medical product development in the United States is unsustainable, taking far too long (from 10-15 years,) and far too much investment (from a low estimate of $350 million to an amortized cost across a full development portfolio of up to $5 billion) to produce a single new drug or biologic. Up to 80 percent of that time and cost is spent in *preclinical* (laboratory and animal testing) and *clinical development* (phase 1, 2 and 3 clinical trials) the parts of the development paradigm that CROs specialize in. Drug development is a complex and multi-faceted effort, requiring capabilities ranging from toxicology and pharmacology to clinical trial management, and ACRO member companies are focused on creating new technologies and business processes to address the time-and-cost conundrum, while at the same time improving the quality and efficiency of the clinical development enterprise.

ACRO applauds the "21st Century Cures" initiative and believes that a multi-stakeholder approach to identifying barriers and creating solutions to our toughest healthcare challenges presents a genuine opportunity for aligning US science and technology capabilities with regulatory policy to benefit not only individual patients but our society as a whole. As companies that represent more than one-third of development spending and are involved in

the conduct of more than half of all clinical trials worldwide, we will focus our comments on pathways to facilitating a new learning and feedback loop across the *discovery-development-delivery* cycle, and potential ways for the U.S. Congress to encourage innovation.

Competing in the Global Innovation Environment

During the Committee's initial Roundtable, one of the topics of discussion was the question of what the U.S. can learn from the policies and incentives being used by other countries to encourage biomedical investment and development innovation. In terms of a public-private partnership that aims to take bold action to accelerate the drug development process, we commend for the Committee's consideration the Innovative Medicines Initiative (IMI,) a joint project of the European Union and the member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA). With a €1 billion Euro contribution from the European Commission and matching (mostly in-kind) contributions from EFPIA, IMI is building research networks and undertaking collaborative research projects to boost innovation in healthcare. The IMI aims to remove bottlenecks in drug development, encourage pre-competitive data sharing and research, and build new business models based on collaboration.

One IMI project, with a budget of over 16 million Euros, EHR4CR (Electronic Health Records for Clinical Research) is building standardized, re-usable and scalable data research networks to create a self-sustaining economic model for re-using EHR data for research purposes, such as determining protocol feasibility and matching patients to appropriate trials. (In contrast, a similar US effort, the PCORnet project of the Patient Centered Outcome Research Institute (PCORI) will cobble together in a one-off fashion 11 clinical data research networks to support observational studies, a model that will lead to data that can't be shared and a network that will always rely on government funding.)

Individual member states of the European Union are also undertaking significant initiatives to accelerate biomedical research. For instance, the Clinical Practice Research Datalink (CPRD) is a UK National Health Service (NHS) offering that provides: de-identified clinical data from some 45 million patient records for data-driven research; a large primary care database for observational studies; and a research network of primary care and other practices that can be utilized for interventional (clinical trials) research.

Today, the U.S. lags considerably in pursuing such bold initiatives. Instead, our health care facilities are compartmentalized and non-interoperable, and our public research apparatus is almost entirely divorced from private-sector capabilities, which leads, inevitably, to constant "reinvention of the wheel."

Several of those appearing before the Committee have endorsed the concept of developing "research networks." We agree with the concept but have some questions about its execution. Certainly, new data research networks could be helpful in conducting outcomes research – areas like comparative effectiveness and drug safety. These studies rely on analysis of data, including "big data." We are skeptical, however, that new research networks cobbled together with government funding will be particularly useful for the conduct of the pivotal clinical trials that lead to the approval of new drugs and treatments. Efficient management of large, multi-site clinical trials requires in-depth knowledge of which investigative sites can recruit the requisite number of patients, follow protocols, and provide reliable data for regulatory review. Today, high-quality, functioning clinical research networks are maintained by leading global CROs and we question the wisdom, as well as the utility, of committing government funding to the creation of new silos of academic research networks to conduct large-scale clinical trial programs.

What Congress Can Do

To provide an example of a step that would break down research barriers, we believe there is an opportunity to **engage private-sector expertise to complement the scientific expertise housed within the NIH, especially for new initiatives like the National Center for Advancing Translational Sciences (NCATS).** The CRO industry possesses project management, data management, patient recruitment and feasibility expertise that simply does not exist within the NIH or among academic researchers. Congressional direction for NCATS to work more closely with industry would, we believe, accelerate this translational research.

Global Tax Competitiveness

With member companies that conduct research around the world, we would suggest specifically that Congress look first at the impact of current U.S. tax policy on the research and development enterprise. With corporate tax rates among the highest in the world and having made little progress toward an equitable system for taxing foreign earnings, the U.S. is increasingly disadvantaged, even in comparison to what may be considered high-tax countries. While there are many reasons to conduct clinical trials on a global basis, including access to populations and markets, U.S. tax policy currently encourages clinical trials to be placed outside the country.

What Congress Can Do

Although it was enacted in 1981, the current R&D tax credit is an "extender" which requires re-enactment each year and so cannot be relied upon by the companies that are making R&D

investments. A related issue is that the R&D credit currently is focused only on the owner of the technology, not on the company that actually does the development work and employs research staff, and so may not incentivize U.S. hiring most fully. These two factors make the U.S. increasingly uncompetitive in relation to other countries, such as the UK, France, Austria and Canada when it comes to the hiring of clinical research staff and the placement of clinical trials. ACRO urges the Committee to work with your colleagues on the Ways and Ways Committee to make the R&D tax credit permanent and to adjust the current limitations on allowing the credit to 'flow through' to the companies that actually perform development work, instead of stopping at the technology owner.

Current U.S. tax law prohibits the R&D credit for "contract research" and further limits to 65 percent the amount of the credit the research sponsor may take when using contract research providers. Increasingly, CROs are making the decisions about where clinical trials are being placed and ACRO members now employ more development staff than the pharmaceutical industry. The employment has shifted along with the research dynamic but tax law has not kept pace. The result is CROs have an incentive to conduct clinical trials in other countries because they cannot avail themselves of the R&D tax credit within the U.S. **Our solution is to simply make the 35 percent of the tax credit that currently evaporates when research is contracted out available to companies performing contract research.** We believe this is a simple and inexpensive policy change that would help keep research jobs and innovation within our borders.

<u>Electronic Health Records (EHRs) and the Discovery/Development/Delivery Cycle</u>

With rapidly increasing adoption of EHRs across hospitals, doctors' offices and other delivery sites and a multi-billion dollar investment by the U.S. government in the "meaningful use" (MU) of such systems, there is no doubt that "big data" (which includes clinical care records, research data, patient-generated and wearable device data, and a range of other data sources) has significant potential to enhance patient safety, improve healthcare, and advance medical science. Within the *development/delivery* cycle, access to EHR data is essential for comparative effectiveness, observational and outcomes studies; and in the conduct of clinical trials EHR data has the potential to facilitate improved protocol design, patient identification and recruitment, adverse event reporting, and the like and thereby shorten the time and cost necessary to accomplish safety and efficacy testing for new biomedical products.

Based on a public opinion poll co-sponsored by ACRO and conducted in May 2013 by Research!America, 53 percent of people hear about clinical trials through the internet or online sources but only 24 percent hear about them from their doctor. Further, only 6 percent of those surveyed said their doctor has ever recommended they participate in a

clinical trial. Yet, 60 percent said a doctor would be their preferred source of information and 72 percent said they would be somewhat or very likely to participate in a clinical trial if recommended by their doctor. By far the easiest way to facilitate this important doctor-patient interaction would be through an EHR system that contains information about relevant clinical trials.

But significant barriers to EHR use, including complicated Informed Consent requirements and concerns about the privacy and confidentiality of individuals, and the lack of a consistent regulatory framework for "secondary use" of health data, have made for very slow progress in the utilization of data to accelerate the discovery/development/delivery loop. Instead, we see isolated experiments in data sharing and re-use, with a preponderance of non-interoperable, purpose-built one-offs, like the FDA's Sentinel Initiative research network.

Information-based research is key to the medical advances that are urgently needed by patients, and central to achieving a transition to an evidence-based, value-driven healthcare system. What is needed is a policy framework that encourages EHR interoperability and data re-use, coupled with regulatory mechanisms that effectively protect (and enforce) data security. We also need to provide incentives for data sharing and fluidity, and a sustainable business model for using EHR data for discovery/development/delivery purposes.

<u>What Congress Can Do</u>

Today a number of agencies and offices – including the Office of the National Coordinator for Health IT (ONC), the FDA, NIH, CMS, HHS's Office for Civil Rights (OCR), the Federal Trade Commission (FTC), the Federal Communications Commission (FCC) and even the National Institute of Standards and Technologies (NIST) – are engaged in developing policies to address various aspects of the "big data" space, from EHR data to telehealth, wearable devices to mobile applications. Because the use and re-use of health and related data is key to accelerating the discovery/development/delivery cycle, we urge the Committee to include testimony from agency and other stakeholders on the topic of "big data" in a future Roundtable.

Two specific recommendations ACRO offers for the Committee's consideration are:

- Congress should encourage **inclusion of new EHR functionalities that will facilitate clinical and data-driven research** as part of ONC/CMS (Office of the National Coordinator/Centers for Medicare and Medicaid Services) **Meaningful Use Phase 3 requirements.** We envision a scenario where EHRs are integrated with clinical trial data from clinicaltrials.gov and can match eligible patients to appropriate research protocols. The EHR would incorporate a "pop up" box to inform the physician of the

availability of a potential clinical trial for their patient. This would greatly speed the recruitment process, reduce development time and cost, and bring treatments to patients more quickly. This may require some small additional appropriation for the National Library of Medicine, which administers clinicaltrials.gov, but we believe this is a small price to pay for the potential billions of dollars in savings in R&D costs, not to mention the added patient benefits.

- Congress should **amend HIPAA to define <u>data research</u> as part of *health care operations* at § 164.506** in order to allow the use of protected health information (PHI) for non-interventional studies, in the same manner that PHI may be used today for quality assessment and improvement activities, outcomes evaluation, and the like.

<u>Driving Innovation at the FDA</u>

One of the questions in the Energy and Commerce Committee's initial white paper on the 21st Century Cures initiative was what the NIH and the FDA have learned from partnerships like the Biomarkers Consortium, the Critical Path (C-Path) Institute, and the Clinical Trials Transformation Initiative (CTTI). As we did in testimony to an FDA Public Hearing on "Modernizing the Regulation of Clinical Trials" in 2012, ACRO is pleased to provide the Committee with a perspective on that question.

In March 2004 the FDA published the report titled, "Challenge and Opportunity on the Critical Path to New Medical Products." The white paper posited the need for "new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs." The report called for a joint effort by industry, academia and the FDA to identify key problems and develop targeted solutions along the "critical path," noting that most of the recent cost increases in the process of getting to new medical products are in the *development* phase – from pre-clinical discovery work through the end of human clinical trial testing, between discovery and launch, in other words.

To advance the Critical Path Initiative, the FDA has supported and continues to support, either financially (to the tune of several million dollars each year) or with personnel or both, a number of public-private collaborations, including the Critical Path (C-Path) Institute, the Clinical Data Interchange Standards Consortium (CDISC) and the Clinical Trials Transformation Initiative (CTTI) and there has been some real progress in development of the "tool box" that supports the biomedical product development paradigm.

For instance, CDISC has more than a dozen data standards and innovations developed, tested and rolled out for use, and C-Path has submitted to the FDA for review more than 60 potential biomarkers, disease models and patient-reported outcomes. Similarly, the NIH Biomarkers Consortium, in which several of our member companies participate, has undertaken data sharing and data mining projects; one project, for instance, analyzed aggregated placebo data from large, industry-funded trials to determine whether the protein adiponectin is useful as a predictive biomarker of glycemic control.

But actual product development remains costly, slow and unproductive. As was true in 2004, it still takes over a billion dollars across a timeline that can take up to 15 years to bring a new biomedical product to market. In fact, many of the themes, if not the specific recommendations, made in the 2004 FDA Critical Path white paper were repeated in the 2012 PCAST report. So we must ask, how much progress have we actually made? And what is standing in our way?

Unfortunately, in assessing the output of agency-funded collaboratives we see very little in the way of projects that might qualify as aiming to 'transform' the *development* paradigm. Instead, we see "research on research" – with surveys, white papers and other publications, recommendations, meetings and educational initiatives, and the like; all of which, we believe, is unlikely to facilitate significant change to current practices, let alone transformation of the enterprise. Simply, understanding that certain practices are wasteful or ill-advised will not, on its own, change those practices.

To illustrate by example: as long as Federal or industry research grants flow to institutions where completion of IRB review averages over two years, without any negative consequences, you can expect that the timeline for IRB review at those institutions will not improve more than marginally. To change behavior the FDA, and the NIH must *expect* the use of central IRBs, not simply endorse their use.

<u>What Congress Can Do</u>

We are optimistic that the early success of the new Breakthrough Therapy designation that was part of FDASIA will have broader implications for drug development. With 156 requests made to the FDA for this designation, and 44 approved, in just over two years there was clearly pent up demand among medical product developers. While by nearly all accounts this program has been successfully implemented by the FDA, we note that it took a specific Congressional directive for the agency to embrace this innovative new pathway.

Time and again ACRO member companies see innovative approaches to clinical trials – which had the blessing of senior FDA officials – derailed by risk-averse auditors in the field. There

must be an innovation culture throughout the FDA to truly drive change in the development process. Our concern remains that in the absence of specific legislative direction and authority, FDA will be hesitant to pursue new innovative ideas that reduce the development time and cost for all new therapies and treatments.

ACRO suggests two actions that would help to re-focus the FDA Critical Path Initiative:

1. **Engage the GAO or other 3rd party to review and prepare a report answering questions such as** – Is the FDA, an agency with scarce resources, receiving an adequate return on its investment in these initiatives? Are these public-private endeavors meeting their objective to produce truly "transformational" outcomes? Might a more collaborative approach with industry produce superior results, at less cost, while the agency can use the funds from these initiatives to, for instance, increase its review staff or invest further in regulatory science?

2. **Direct that the FDA appoint a Chief Innovation Officer** who shall be responsible for overseeing the Critical Path Initiative and will have the authority to agree to and enforce new, innovative approaches to drug development.

In Conclusion

Today CROs employ more scientists and research personnel in *development* than do the pharmaceutical and biotech companies that typically initiate the process of *discovery.* And we are increasingly involved in the application of data analytics to the outcomes, safety, comparative effectiveness, and other data derived from the *delivery* of (and payment for) health care.

In the clinical trial process, CROs operate in the nexus between research sponsors and regulators. So, we have a unique appreciation for the many competing interests that must be balanced in the conduct of clinical research – speed, cost, efficiency, innovation, transparency and, most importantly, patient safety.

A full 10 years since the publication of the FDA *Critical Path* white paper, we have reached a stage where bold action, leadership and accountability are required to move the drug development enterprise forward so that we all can benefit from new therapies and treatments sooner. To do less is to remain stuck in a product development model that is too costly, too long and simply does not produce the number of new products needed. The task at hand is both large and enormously important, and ACRO is fully prepared to respond to the Committee's Call to Action to create a scientific, regulatory, business and policy environment that will indeed lead to 21st Century Cures.

ACRO thanks the Committee for the opportunity to provide this comment and we look forward to continued dialogue. Please do not hesitate to contact us for further information at any time.

Respectfully,

Douglas J. Peddicord, Ph.D.
Executive Director

Partnership to Improve Patient Care
21st Century Cures Initiative: Comments to the House Energy and Commerce Committee
June 16, 2014

The Partnership to Improve Patient Care (PIPC) supports the Committee's 21st Century Cures Initiative and the goals of accelerating discovery, development, and delivery of innovative treatments for many diseases that do not currently have treatment options. We applaud the Congress, and in particular Chairman Fred Upton and Congresswoman Diana DeGette for leading this bipartisan effort. Thank you for seeking comments to address this issue. We are very pleased to have this opportunity to provide input.

Comprised of 48 organizations and growing, PIPC has recognized the importance of promoting health care delivery systems that support the related goals of patient-centeredness and medical progress through innovation and ongoing clinical research and analysis. Our founding principles on comparative effectiveness research (CER) emphasize these goals by calling for strong patient access protections in the use of CER, explicit alignment of CER with innovation, and improved communication and recognition of the value of innovation. As we seek to address continued, significant areas of unmet medical need and to realize significant opportunities for improving the efficient delivery of high quality care, innovation means many things -- new treatments, improvements to existing treatments, efficiencies in the delivery system, higher quality care and overall a reduction in the economic and health burden of disease.

As health care decision-makers increasingly are adopting CER-based evidence and tools, PIPC has advocated for a delivery system that supports informed patient choice from a range of treatment options and explicitly recognizes and incentivizes innovation as an element of patient-centeredness.

The Committee is taking a comprehensive approach and PIPC applauds its work. We believe that to effectively support innovation, the Committee must consider both regulatory reforms to accelerate innovation and focus on supporting a delivery system that can accommodate and provide patient access to these advances. Innovation and access are equally important to patients.

Our recommendations below are based on our experience with advancing patient-centered CER. Thank you for your consideration of these principles:

- Explicitly align policy with innovation: If existing regulatory or reimbursement policy is a barrier to either the development of improvements in the science or patient access to these advances, then those barriers should be re-evaluated and removed;
- Provide a meaningful voice to patients: In all appropriate venues where policy around the value of innovation is being measured, the patient voice should be included and ultimately reflected in the decision-making process;
- Protect against policies that impose blunt access restrictions to medical options that are best suited to individual patients: Medical management tools should be patient-centered and not based on one-size fits all evidence standards;

- Foster informed choices from the range of clinical/care options: Patients and providers can both advance innovation and benefit from it when reliable, accurate information is more readily available through modern information sharing tools;
- Incorporate constructs that were designed with the help and expertise of the patient community: PCORI created a new way to develop and design patient-centered outcomes research but the statute also includes protections around the misuse of innovative research;
- Ensure transparency and accountability as payment and delivery models evolve (i.e. ACOs and alternative payment models);
- Make the conversation about innovation as broad as possible to maximize the value to patients: It should be holistic and view the needs of patients across the care continuum.

PIPC greatly appreciates the opportunity to share our high-level principles and recommendations with the Committee. We are excited and grateful for your commitment to this critically important dialogue around how to support innovation and improve health care overall. PIPC is developing a more comprehensive white paper on advancing innovation through evidence-based, patient-centered care in alternative payment models and looks forward to sharing this with the Committee very soon.

June 12, 2014

Honorable Fred Upton
Chairman
Energy & Commerce Committee
House of Representatives
Washington, D.C. 20515

The Honorable Diana DeGette
Co-Chair, 21st Century Cures Initiative
Energy & Commerce Committee
House of Representatives
Washington, D.C. 20515

Dear Chairman Upton and Representative DeGette:

Food Allergy Research and Education (FARE), the leading nonprofit organization focused on food allergies, is pleased to comment on the FARE strategy for food allergy research as part of the Energy & Commerce Committee's 21st Century Cures Initiative fact-finding effort.

FARE, the result of a 2012 merger between the Food Allergy & Anaphylaxis Network and the Food Allergy Initiative, is dedicated to investing in world class research to find a food allergy cure. While we pursue the cure, we seek to ensure the safety and inclusion of individuals with food allergies.

The food allergy problem presents different research and public health challenges from many of the rare diseases that the committee has focused on through the 21st Century Cures effort. Food allergies are not a rare disease, because as many as 15 million Americans have such allergies. There are no effective FDA approved treatments of food allergies, beyond avoidance of problem foods and treatment of anaphylaxis.

However, we believe that the research community is poised to make important advances in understanding and treating food allergies. The experience of some of our peers in the nonprofit research community – the development of clinical trials networks, establishment and utilization of patient registries and biorepositories, and financial support of young investigators to build a skilled research community – is informing the efforts of FARE to expand private support for food allergy research.

We also believe that, in order to attract biotechnology and pharmaceutical interest in food allergy research and development, FARE must develop sophisticated research tools and resources to reduce the risks associated with food allergy research.

Finally, there are important steps that Congress can take to support the development of a strong food allergy research effort.

Food Allergies as a Public Health Problem

Up to 15 million Americans have food allergies. Studies support the anecdotal observation that the number of Americans with food allergies is growing rapidly. A May 2013 report from the Centers for Disease Control and Prevention (CDC) found that the prevalence of food allergy among children increased 50 percent between 1997 and 2011.

The management of food allergies today combines strict avoidance of problem foods and treatment of reactions with self-injectable epinephrine and rapid transport to the emergency room. This is an imperfect strategy for management of food allergies, because accidental exposures are common. In addition, the economic, social, and psychological burdens associated with strict avoidance of problem foods are great, with the impact felt not just by the affected individual but also by families who must adjust their lifestyles to accommodate food allergy management.

The management of food allergies imposes a serious financial burden on families, and society also bears a substantial cost associated with food allergies. One recent study estimates the annual cost of managing each child with a food allergy at over $4,000 per family, or over $25 billion nationally.

There is a critical need for additional surveillance to understand the prevalence of food allergies and the burden that food allergies pose.

The Food Allergy Research Challenge

Results have been published from more than a dozen clinical trials of oral immunotherapy (OIT), with the results suggesting that about 70 to 80 percent of those with food allergies can be desensitized for some period of time. However, there were substantial differences in the protocols of these studies, conducted over a range of clinical trial sites. Although the studies are very important in advancing the field, a more consistent and well-coordinated approach will be necessary to establish the safety and efficacy of OIT in the treatment of food allergy.

There are many unanswered, fundamental questions about food allergies. For example, we do not understand why food allergies are more common today than in the past. We have not established the prenatal and early life determinants of food allergies, and we do not understand the wide variations in food allergies, including the different reactions of individuals to different foods and the range in severity

of allergic reactions. We are persuaded that a food allergy biorepository that combines biospecimens with clinical data from large numbers of patients would be a valuable tool in this basic research pursuit.

Food allergy poses a serious disease burden, but there are still relatively few researchers in the field. Although the National Institutes of Health (NIH) investment in food allergy research does match the disease burden and public health burden posed by food allergy, there are also limits on the quantity and quality of investigator-initiated received by NIH. Researchers also find themselves in a funding quandary, unable to produce the preliminary data that are in practice necessary for a strong research funding application. FARE intends to follow the example of many of its colleagues in the non-profit research sector by supporting young investigators who are engaged in food allergy research, both to produce solid scientific studies and to foster a cadre of sophisticated researchers in the field.

The FARE Plan

In April 2013, FARE held a research retreat of leaders in food allergy research and developed a strong ten-year plan for food allergy research. The organization's fundamental goal for food allergy research is expressed by this vision statement:

> By 2023, we will be able to accurately diagnose food allergy and predict individual disease progress and response; we will be able to offer patients effective therapies beyond avoidance; we will do this informed by a deep biological understanding of food allergy and via a vibrant community of investigators.

To achieve this goal, FARE will pursue three specific research efforts:

- Develop a strategy and infrastructure to test clinical hypotheses in man and advance clinical research rapidly.
- Develop the scientific understanding, tools, and resources necessary to facilitate research that will build a pipeline of future therapies.
- Actively attract and develop outstanding investigators to the field of food allergy.

In all of these efforts, FARE will be guided by the advice of leaders in food allergy research and the experience of other successful research foundations that have created clinical trial networks, pioneered the development of tools, such as biorepositories and registries, and nurtured a community of investigators.

Public Sector Role in Food Allergy Research

Although FARE and the food allergy community are assuming a leadership role in developing the tools and resources for a strong food allergy research and development effort, public investment in all phases of food allergy research is critically important. The burden of food allergy is great for the individuals affected and for society, and it is appropriate for the public research program to include a strong food allergy component.

We applaud recent efforts by NIH to create structures and support systems to encourage public-private partnerships in therapy development. Leveraging NIH dollars in this manner is a solid strategy. However, there is still a great need for NIH leadership on basic research questions, and we urge NIH leaders to pursue the elusive but critical balance between the basic and applied research that will advance basic knowledge of diseases and also foster therapeutic development.

The Response of Congress

We appreciate the efforts of the committee to focus on optimal strategies for therapeutic development for a wide range of diseases. We note that there is a heavy emphasis on the development of therapies for rare diseases, an emphasis that probably arises from the assumption that such diseases and conditions are not attractive targets for biotechnology and pharmaceutical industry investment. While we understand this particular emphasis, we urge that there be appropriate attention to diseases that are not "rare" but that confront some of the same research challenges – including obstacles to strong private industry investment – as rare diseases.

The Food and Drug Administration Safety and Innovation Act, for example, included special emphasis on rare diseases. In addition, NIH has directed significant attention to the development of clinical trials networks for rare diseases. We applaud those efforts but at the same time recommend that some of the same attention, strategies, and funding that is directed to rare disease research might also benefit other fields where research investment lags and research tools are underdeveloped.

We also urge Congress to consider an increased level of NIH funding and stability in NIH funding. FARE is undertaking a strong program to attract, fund, and mentor food allergy researchers. However, there is no doubt that questions about the reliability of NIH funding have an effect on the willingness of researchers to enter and remain in a new field. FARE can play an important role in building a strong group of food allergy researchers, but the organization cannot do this alone.

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FARE appreciates the opportunity to participate in the committee's 21st Century Cures process, and we look forward to the ongoing discussion about foster therapeutic development for diseases of the 21st century.

Ian C. Read
Chairman of the Board
Chief Executive Officer

Pfizer Inc
235 East 42nd Street, New York, NY 10017
Tel 212 573 3759 Fax 212 309 0567
[redacted]

June 19, 2014

The Honorable Fred Upton
Chairman, Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
U.S. House of Representatives
2368 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton and Congresswoman DeGette:

On behalf of Pfizer, I am pleased to provide comments on the 21st Century Cures Initiative: A Call to Action White Paper.

Since our founding in 1849, Pfizer has been and remains committed to finding cures for the many diseases afflicting our population. We developed and produced a vaccine at the turn of the 20th century that contributed to the world wide eradication of small pox. In 1944, Pfizer's ability to mass produce penicillin helped save the lives of thousands of troops who were injured during the Allied invasion of Normandy. In the decades since, we have led the way in bringing to the market advances in treatments for heart disease, infections, depression, and pain. Those medicines have improved health, reduced costs and extended productive lives for millions of people. Many of these medicines are now available in a generic form at a very low cost, creating an enormous benefit to society. With an environment that supports innovation, this cycle will continue for many other diseases, including cancer. Behind these therapies is the process that brings them to patients which you have described in the White Paper as Discovery, Development, and Delivery.

That process has changed dramatically over the past 20 years, due in large part to technological advances, notably the mapping of the human genome and our fundamentally better understanding of human biology, which has enabled researchers to develop new therapies targeted at a variety of diseases with large unmet medical needs. This includes Pfizer's Xalkori, the first medicine approved for patients with an ALK positive gene mutation with locally advanced or metastatic non-small cell lung cancer. Achievements in the Discovery phase have led to advances in Development where we are able to utilize tools like biomarkers and surrogate endpoints to help us demonstrate the safety and efficacy of a new product.

The first two phases of the process, Discovery & Development or Research & Development (R&D), are the lifeblood of Pfizer. It takes on average more than $1 billion and 12-15 years to research and develop a new medicine. Only approximately 1-in-10,000 compounds that enter the drug discovery phase is approved by the Food and Drug Administration (FDA). Our R&D pipeline is focused on areas where Pfizer has a unique opportunity to address unmet needs, such as cancer, chronic inflammatory and autoimmune diseases, vaccines, oncology, neuroscience and pain, cardiovascular and metabolic disease and rare diseases.

Since launching a comprehensive R&D turnaround effort three years ago, we are working toward a future where R&D is consistently delivering important therapies for the patients who are counting on us. We have seen steady progress in our late stage pipeline that includes positive clinical data presentations, submission of marketing applications, regulatory approvals, and new product launches.

By collaborating with partners in new ways we are advancing our purpose of innovating to bring new therapies to patients. This includes launching and supporting the Centers for Therapeutic Innovation, which works in partnership with academic institutions to advance basic research to clinical development. In another example, Pfizer and the non-profit drug discovery and development affiliate of the Cystic Fibrosis Foundation have a research collaboration to speed the discovery and development of potential therapies. FDA also has the potential to be an engine for innovation. To realize that potential the review process must become more efficient and must employ a comprehensive risk benefit analysis focused on the patient.

We also look beyond FDA approval to ensure that payers recognize the value of our medicines as decision making on healthcare is increasingly focused on cost. While innovative new medicines and vaccines are powerful levers for stemming the tide of illness and disability that threaten an aging population and can represent great value, we are challenged by health insurance management tools designed to contain costs, but not necessarily to ensure long term health and financial sustainability. Payer reimbursement provides a powerful signal to investors in R&D, and as such either limits or fosters innovation.

Drugs, unlike any other healthcare sector, have built-in cost containment in the form of patent expiration. We file our patents well before FDA review. By the time we have submitted an application to the FDA, the patent life has already begun ticking away, making an effective and efficient regulatory review process all the more important to sustaining innovation. Biopharmaceutical companies like Pfizer typically have at most between 11-14 years from approval to earn a return on our investment in a new compound before the patent expires and generic competition enters the market. Only around 2 in 10 medicines are profitable and the revenues from these medicines, during the time of patent protection, fund our research efforts for future medicines. After the limited period of time of market-based prices for new medicines, the global health care system ultimately receives low cost generics forever. But without innovation, there is no long term gain for society.

For example, Lipitor (atorvastatin) and other statins, which were highly commercially successful and funded innovation in cancer and other research, saved 40,000 lives, reduced 60,000 heart attacks and reduced 22,000 strokes in one year alone, generating far more benefit to society than was paid for the medicine even before generic competition became available. Today, 12 million people in the U.S. take inexpensive generic atorvastatin each year, reaping enormous societal benefit from Pfizer's investment.

Over the next decade, several Pfizer medicines will lose patent protection generating significant cost savings to patients and the overall health care system. This benefit can only be achieved if innovative companies like Pfizer have the incentives necessary to produce the next round of cutting edge therapies that will eventually be available at low cost.

In the attached document, Pfizer shares its views on the important questions and issues raised in the Call to Action White Paper. While we face ever increasing challenges, we remain steadfast in our mission: *Innovate to bring therapies to patients that significantly improve their lives.*

Sincerely,

[redacted]

Ian C. Read

Attach.

21st Century Cures Initiative: A Call to Action White Paper Response
June 19, 2014

SUMMARY OF KEY PRIORITES

Discovery

- Continue support for pre-competitive partnerships, such as the Accelerating Medicines Partnership, that identify and validate promising biological targets.
- Accelerate larger scale partnerships to connect and harness the power of Electronic Medical Records and genomic data. Promote the analysis of in-depth molecular/genomic data (proteomics, metabolomics, transcriptomics, and epigenomics) through development of enabling technologies.
- Ensure that graduate science programs are focused on training future talent on the integration of life sciences, computing, and leadership - the skills needed to maintain U.S. dominance in R&D.
- Provide stable and substantial increased funding to the National Institutes of Health (NIH) so that they have sufficient budget to continue to study the complex biology of disease and attract world class scientific talent.
- Examine the value of increased regulatory exclusivity for small molecules.

Development

- Accelerate the development and regulatory acceptance of novel clinical trial designs and drug development tools. Ensure that FDA makes full use of available regulatory approval pathways/mechanisms to expedite the development and approval of new therapies.
- Increase efforts to recruit patients, particularly diverse patient populations, to participate in clinical trials.
- Leverage new technologies to streamline data collection in clinical trials.
- Improve the efficiency of the current regulatory approach to post marketing study obligations.

Delivery

- Ensure that health insurance benefits are designed to foster good health, not just contain cost. Benefit design should encourage the use of the most efficient and effective medical services first, including treatments with a higher up-front cost that could result in long term better health, less suffering, and lower utilization of expensive acute care.

- Support the development of health-based, rather than volume based payment to healthcare providers by improving point of care systems where providers can measure health outcomes in real time, have access to validated quality measures, and have a means to be rewarded for improving health and patient satisfaction.

- Modernize the current coding and payment system to support the introduction of new medical technologies, such as gene therapy and precision medicines, that currently have no consistent coding or payment mechanisms.

- Ensure that all healthcare stakeholders have access to all relevant data available about healthcare treatments including medicines to enable better decision-making.

- Examine the need to provide better product liability protection for manufacturers of FDA approved innovative prescription medicines and the doctors who use them.

DISCOVERY

Unlocking the Power of Discovery Research

The sequencing of the human genome and the growing identification of genes associated with major disease are improving our understanding of human health. While this growing body of knowledge offers great promise, identifying and validating promising biological targets, such as a receptor, enzyme or protein that are implicated in the disease, continues to be one of the greatest challenges for our industry to translate emerging science into medicine. Basic scientific research carried out by academia, government and industry explores our complex biology and the causes of diseases and works to identify these targets.

The biopharmaceutical industry is largely focused on developing new medicines that act upon these receptors or enzymes in order to create improvements in the disease condition and in patient health. However not all discoveries of potential targets are directly applicable to the development of new medicines. In fact, the vast majority of potential targets discovered in basic science research must still be revalidated by industry as the first step in the discovery research process. In this way, the translational research process begins -- transferring knowledge of underlying disease biology into a research hypothesis and hopefully new important medicines that are validated by 10-15 years of discovery research, preclinical research and clinical development.

By improving the quality of targets, the biomedical research community and the public may benefit from higher clinical trial success rates. Pfizer commends the Accelerating Medicines Partnership for providing pre-competitive cross-sector partnership opportunities to identify and validate promising biological targets in type 2 diabetes, autoimmune disorders and Alzheimer's disease. Another high potential opportunity is to accelerate the generation of large scale, in-depth genomic data linked to electronic medical records. Through the federally-supported rollout of electronic medical record (EMR) systems across the nation, we can harness the power of big data and genomic studies to better understand diseases and improve the success rate of new medicines.

The NIH is providing a preliminary foundation to connect the use of big data with genomics. The Electronic Medical Records and Genomics (eMERGE) Network promotes collaboration among researchers from institutions such as Vanderbilt University and Geisinger Health Systems, by offering access to a large pool of patient data connected to genetic samples. Better analytical tools will accelerate the development of biomarkers, define patient populations and identify new indications for medicines. In this regard, advanced analytical tools and cell technologies must be developed to fully capture the complex biological systems underpinning disease and to enable science to bridge from molecular analysis to function.

Additionally, the ongoing development of EMR standards to further the interoperability of disparate systems holds important implications for medical and biopharmaceutical research stakeholders as they work in partnership to advance high quality medical care and address unmet medical needs.

Finally, to realize the potential of big data and genomics, we must develop and support scientific talent to gain knowledge that will lead to new treatments and cures. This requires a high quality education and well-funded NIH. Our educational system should educate and graduate scientists with expertise in both computational science and biology. Stable and robust NIH funding is needed to further understand the complex underpinnings of disease, encourage talent development, and lead the development of additional private-public partnership programs such as the Accelerating Medicines Partnership. In the past 10 years, NIH has lost 20 percent of its purchasing power, reducing incentives to pursue careers in scientific research. Pfizer believes these steps are critical to improving public health and maintaining our country's leadership position in biomedical science.

Incentivizing the Discovery of New Therapies

Drug discovery and development is an inherently risky and resource intensive process – for every 5,000 to 10,000 experimental compounds considered, typically only one will gain FDA approval. Therefore, intellectual property (IP) protections must ensure that biopharmaceutical companies have an opportunity to recoup these extremely risky investments in life-saving medicines and provide incentives to support further innovation. This protection is vital in the United States and with all of our trading partners.

Current regulatory exclusivity for small molecules, governed under the Hatch Waxman Act, provides originators with five years of exclusivity for new chemical entities and three years for supplemental applications. However, since the enactment of Hatch Waxman over thirty years ago, the cost of drug development has skyrocketed and the complexity of those diseases with significant unmet medical need (*e.g.,* uncontrolled diabetes, Alzheimer's disease, schizophrenia, chronic pain) makes R&D significantly more challenging.

Congress recently recognized the value of additional exclusivity in incentivizing R&D when it passed the Generating Antibiotics Incentives Now ("GAIN") Act, which increased the exclusivity period for qualifying antibiotics to 10 years. Given the challenging R&D process, Pfizer recommends that Congress consider increasing exclusivity for small molecules to provide additional opportunities to bring about new treatments and cures for diseases with high unmet need.

DEVELOPMENT

It is important for the government to continue to work with biopharmaceutical companies and academic partners to leverage recent advances in targeted medicine and health information technology to modernize and accelerate the clinical trial process. Some successful ongoing partnerships include the National Center for Advancing Translational Sciences (NCATS) at the NIH, and in particular, its Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) program, and the Clinical and Translational Science Award (CTSA) program's Clinical Trial Coordinating Center (C4) with its comprehensive coordinating platform for multi-site clinical trial conduct. It is also essential to have a regulatory environment in which FDA uses all of its existing authority to support expedited drug development, when scientifically appropriate.

Accelerating the Development and Regulatory Acceptance of Novel Clinical Trial Designs, Expedited Approval Pathways, and Drug Development Tools

While the traditional model of standard clinical testing involving three phases of large scale, controlled trials is still necessary in many cases, recent advances in drug development have produced drugs that show a dramatic benefit very early in the clinical testing process and warrant a different clinical trial approach, particularly when existing treatment options have limited efficacy. For example, a number of cancer therapies that have shown a substantial treatment effect early in development, including Pfizer's lung cancer therapy Xalkori (crizotinib), have been approved through the accelerated approval pathway based on the use of surrogate endpoints in a single arm trial (SAT), in which a sample of individuals with a defined medical condition is given the investigational medicine and monitored over time to observe their response. However, outside of the oncology setting, challenges in gaining regulatory acceptance of flexible clinical trial designs and novel surrogate endpoints have prevented the use of the accelerated approval pathway for many conditions, including many rare diseases.

FDA has ample authority to evaluate new drugs on an expedited basis and permit flexible clinical trial designs. The mechanisms with the potential to most significantly shorten the clinical development timeline are the accelerated approval pathway and the new "breakthrough therapy" designation, established by Congress in 2012 in FDASIA. The accelerated approval pathway, available since 1992, permits FDA to approve a drug based on one or more surrogate endpoints that are reasonably likely to predict clinical benefit, provided that the sponsor agrees to conduct a post approval trial (s) to confirm benefit. This can dramatically speed access to a new drug when it might otherwise take years of study to demonstrate a survival benefit or other long term outcome. Sponsors can now also apply for a "breakthrough therapy" designation for a drug intended to treat a serious or life-threatening conditions where early clinical evidence shows that the drug may offer a substantial improvement over existing therapies. Once a drug has been granted breakthrough therapy status, FDA commits to work closely with the drug's sponsor to create an efficient development plan and facilitate its review.

More legislation to create additional approval pathways is not necessarily the answer. Instead, concerted efforts should be spent to ensure that FDA uses its existing regulatory flexibility whenever scientifically appropriate and there is a consistent approach to using the tools across review divisions. Pfizer has observed the accelerated approval pathway used more frequently in the oncology and vaccines areas, and less so in other therapeutic areas, where we believe there are additional opportunities to leverage the pathway particularly for drugs or biologics intended to treat rare diseases.

While there are circumstances where scientific uncertainty about the appropriate surrogate markers for a condition prevents the accelerated approval pathway from being used, Pfizer is concerned that in some cases, a review division's lack of familiarity with operationalizing the pathway may perpetuate a continued reluctance to use it. Additionally, the decision to permit the use of a new surrogate endpoint requires the Agency to make a careful scientific evaluation and take some degree of thoughtful, calculated risk, and review divisions must have sufficient resources to complete the evaluation and feel supported by their management to take this type of risk. Congress should press FDA to remove any internal barriers that may exist in using the accelerated approval pathway and other existing tools/mechanisms to expedite drug approval and make sure that agency reviewers across all divisions are comfortable using them when appropriate.

The expedited development and qualification of drug development tools (DDTs) including biomarkers and Patient Reported Outcome (PRO) measures for use in regulatory decision-making and/or for inclusion in product labeling can galvanize drug development and has been a shared priority for industry and the FDA. While some progress has been made, less than a dozen qualified biomarkers and PROs are listed on the FDA Drug Development Tool web page. Congress should request an analysis to understand the impediments to the regulatory qualification process. Congress should also consider working with FDA to provide a means to expedite the regulatory qualification process, potentially to include funding retrospective qualification of broadly accepted DDTs that have successfully been used in accelerated approval decisions.

Encouraging Participation in Clinical Trials

Challenges with patient recruitment are one of the biggest causes of clinical trial delays. Patients who are not treated at a major medical center may not be aware of opportunities to participate in research. Pfizer recommends that Congress consider a comprehensive public awareness campaign directed to patients and their healthcare providers to discuss the importance and benefits of participating in clinical trials and provide online information about ongoing trials in an easily searchable, consumer-friendly manner. Additionally, Congress should explore providing incentives to encourage healthcare providers to talk to patients about clinical research and refer them to clinical studies. Both efforts should take into account the need to increase participation by diverse patient populations, including minorities and pediatric patients.

The use of a placebo arm in a clinical trial can hamper patient recruitment because some patients are unwilling to participate in a study unless they will receive an active treatment. TransCelerate Biopharma is leading an initiative to aggregate existing placebo arm data from previously conducted studies in various disease states, with the goal that these data can be used as corroborative evidence to reduce the need for large placebo control arms. Congress should encourage the FDA to become involved in these discussions early in the process to facilitate regulatory acceptance of studies performed using this approach.

Leveraging New Technologies to Streamline the Collection of Clinical Trial Data

Pfizer and other companies are exploring how advances in health information technology and mobile devices can be leveraged to make the collection of clinical trial data more efficient. For example, instead of requiring a study investigator to complete traditional case report forms, data for clinical trials could be sourced from prospective EMRs that are routinely completed by the treating physician as part of a patient's healthcare. This approach can eliminate the burden on clinical site staff of completing separate clinical study specific forms and enable the study to be run more quietly alongside the provision of healthcare. Advances in mobile sensors and wearable devices can help to track patients' physiological data (*e.g.*, heart rate, temperature) and further streamline the collection of information for investigators and clinical study sites. While sponsors have made some efforts to incorporate these technologies into clinical trials, they will hesitate to fully incorporate them into registrational studies unless they can be assured that regulators will accept data generated using these methods. Congress should encourage government agencies, the biopharmaceutical industry, and academia to work together to develop standards for the use of EMRs in clinical research, prioritize the use of new technologies and take the steps necessary to achieve regulatory acceptance of these technologies in clinical studies.

Exploring Greater Efficiencies in Postmarketing Study Obligations

Postmarketing requirements (PMRs) and postmarketing commitments (PMCs) are tools FDA uses to have sponsors gather safety and efficacy information about drugs after they are approved. Examples include requirements to conduct confirmatory effectiveness studies for drugs approved under the accelerated approval pathway, pediatric studies under the Pediatric Research Equity Act (PREA), and safety studies. The number of PMRs appears to be increasing, particularly since FDA was granted new authority to impose safety PMRs with the passage of FDAAA in 2007, and a significant portion of Pfizer's phase 4 clinical research resources is now spent satisfying post marketing study obligations.

While such studies can provide valuable information to support the public health, Pfizer is concerned that the process for determining what information is needed for these studies and appropriate study design(s) lacks transparency and results in additional time and expense for sponsors. For example, it can take many months to obtain agreement on a protocol for a required study, which can take valuable time away from the conduct of a study or in some cases lead to changes in a study for which planning has already been initiated. Particularly in the pediatric realm, sponsors may be asked by the agency to conduct studies that are not feasible, leading to delays in recruiting patients. Finally, sponsors should be permitted to use existing, real world data available in medical claims databases or registries to address post marketing study obligations wherever scientifically appropriate, as this approach is more efficient and can result in significant cost savings.

Pfizer suggests that Congress consider the following with respect to PMRs/PMCs: (1) establishing PDUFA goals for timeliness of review of study protocols; (2) establishing new initiatives or accelerating existing initiatives for stakeholders (including FDA, industry, and academia) to develop innovative study designs for pediatric studies and to harmonize FDA and EMA pediatric study requirements; (3) establishing a well-defined and transparent process within FDA, with the help of external experts, for determining clear study objectives and the most appropriate study designs to satisfy those objectives; and (4) establishing a mechanism for FDA to periodically re-evaluate the continued need for a study and lift the requirement if no longer scientifically warranted.

The cost savings realized from conducting these studies more efficiently can enable companies to spend more of their research budgets on developing new innovative medicines or new indications for existing medicines.

DELIVERY

The cycle of innovation does not end when a medicine is approved by the FDA -- in many ways, it is just beginning. Innovation in healthcare delivery fosters an effective and sustainable healthcare system by ensuring that patients are receiving the appropriate treatments for their condition, to support their health and to manage cost efficiently. Ensuring that the medical needs of individual patients are met through both treatment and prevention provides societal benefits that are realized through reductions in healthcare costs, less disability and morbidity, increased productivity and reduced burden on caregivers. All healthcare stakeholders have an obligation to address unmet medical needs. In order to reach this ideal, health insurance benefits, heath information technology and provider payment systems should be designed to encourage health and control costs in a holistic manner considering the benefits and risks of the treatment over time and across sites of care. This includes:

Ensuring Insurance Coverage Is Designed To Manage Health

A primary purpose of health insurance is to have predictable healthcare cost, but services most needed by patients with significant illness are more and more limited. Because they can no longer base prices on the health of the beneficiary, insurance plans increasingly exclude certain hospital networks, specialist physicians, and specialty drugs from network coverage, or impose hurdles such as paperwork or high patient cost sharing for those services. This can result in the highest need patients not receiving the care best suited to their condition and can lead to costly outcomes such as hospitalization, lost productivity or unneeded suffering and shorter lives. Ideally health insurance benefits should be designed to encourage the use of the most efficient services first, resulting in lower utilization of expensive acute care and better health outcomes. Solutions include greater use of Value Based Insurance design approaches, tools that make it easy for patients to use to compare formularies and costs, clear appeals processes for patients and providers to request affordable access to care, and limits on out of pocket spending for patients that are grounded in evidence rather than to meet a budgetary goal.

Aligning Provider Payments with Health Outcomes

Innovation in payment and delivery reforms including quality bonuses and provider risk sharing shows promise for better health outcomes and cost containment. However, many therapeutic areas lack quality measures that have outcomes relevant to patients and the process for updating those measures is slow. Moving toward a system where providers of healthcare can measure health outcomes across sites of care, have validated measures that include patient input, and have a means to be rewarded for improving health and patient satisfaction will enable a movement away from volume based payment to health based payment. Quality measures will enable patients to choose health plans and health providers based on outcomes that are relevant to them.

This hinges on both information and process improvements which include interoperability between EMRs, clear and correct formulary information in EMRs, integrated datasets between payers, the development of tools that help physicians use EMR at point of care, and a transparent and swift process for validating quality measures with input from patients and providers.

Ensuring New Treatments Aren't Needlessly Delayed by Today's Payment Systems

Twenty-first century cures aren't useful if patients can't get them through their insurance plan. As medical innovations are developed and enter the healthcare system, the appropriate coding and payment systems must be in place to enable their use in clinical practice. Incomplete or inadequate coding has already been a barrier for molecular diagnostics and genetic testing. Reforming the current coding and payment system is crucial to the success of new medical technologies, particularly for highly innovative therapeutic options such as stem cell and gene therapy, precision medicines and regenerative medicines that currently have no consistent coding or payment mechanisms.

While the FDA has mechanisms to recognize an unmet medical need, payers often don't have efficient mechanisms to recognize these same new therapies. If the FDA determines that a medicine warrants accelerated review or is deemed a breakthrough therapy than payers, providers and other stakeholders should also take steps to enable affordable patient access. Payer systems need to be enhanced or, in some cases, created to help ensure patient access to breakthrough therapies for unmet medical need. For example, Pfizer is currently studying a drug for sickle cell disease that is given in the inpatient setting. We are hopeful that it will provide a significant improvement in the health and productivity of a largely African American patient population that hasn't seen any innovation in decades. And yet, current provider reimbursement mechanisms in the Medicare and Medicaid programs would hinder access to this treatment.

Ensuring Health Care Decision Makers Have Access to All Relevant Information Available about Medicines

Ensuring access to real world data captured in EMR, medical claims databases or registries is vital to nearly all stakeholders and can provide crucial information by elucidating unmet needs in our current system and information about the efficiency of healthcare delivery, and helping to demonstrate value, efficacy, and safety. Releasing more of the data housed in government datasets to qualified researchers, and connecting it across multiple sources could dramatically improve the innovation cycle, as unlocking and analyzing data will enable better decision making between patients and physicians and innovation in care delivery and new treatments.

FDA's regulations pertaining to manufacturers' ability to communicate about their products currently permit manufacturers to share only that data that meet the "substantial evidence" standard, which FDA has construed to require at least one, and usually two, adequate and well controlled studies. The result of this restriction is that manufacturers are prohibited from freely sharing other types of data that are highly relevant to patient care and routinely relied upon by physicians and insurers, including meta-analyses that evaluate data from a number of controlled studies, observational studies that evaluate the "real world" use of a product over time, and subpopulation data from clinical trials, including information about the effects of medicine by race and gender.

Further, FDA's regulations operate selectively, prohibiting only the product's manufacturer from discussing this data, but not restricting other participants in the health care field, and this creates an asymmetrical situation where the manufacturer is not able to fully participate in open scientific discourse about its therapy. This type of speaker-based restriction also runs counter to current trends in First Amendment case law.

Pfizer urges Congress to consider legislation and/or press FDA to revise its regulations to adopt an approach that is consistent with the First Amendment and similar to what is permitted throughout Europe and most other regions in the world, whereby manufacturers can share a broad range of clinical data available for their products provided they provide appropriate context for the data and present them in a truthful and non-misleading way. Robust discourse about all of the clinical data available for medicines will help health care providers and insurers make the best treatment decisions for their patients.

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Finally, Pfizer urges Congress to examine the need to provide better product liability protection for manufacturers of FDA approved innovative prescription medicines and the doctors who use them. Given its medical and scientific expertise, the FDA is the best authority to weigh the benefits and risks of prescription medicines, and ensure that those benefits and risks are appropriately communicated in product labeling. The current legal environment permits the FDA's decisions to be second guessed on a state by state basis and creates a tremendous financial burden for manufacturers, who spend billions of dollars a year defending state product liability claims. Additionally, the current environment provides enhanced product liability protection for generic drugs, while innovative prescription medicines do not receive this protection. Savings achieved from addressing this issue and eliminating this disparity would provide manufacturers of innovative medicines with additional funds to invest in their research and development efforts.