



House Committee on Energy and Commerce

21st Century Cures

Public Comments

Submitted by:

The Roundtable on Critical Care Policy

President, Stephanie Silverman

May 15, 2014

The Roundtable on Critical Care Policy (Roundtable) appreciates the opportunity to provide the Energy and Commerce Committee with comments on the 21st Century Cures initiative and the white paper, *21st Century Cures: A Call to Action*.

The Roundtable provides a forum for the nation's leaders in critical care and public health to advance a common federal policy agenda to improve the quality, delivery and efficiency of critical care in the United States. Our not-for-profit organization brings together a broad cross-section of stakeholders, including renowned critical care clinicians, academia, public health advocacy interests and industry.

Critical care medicine is the care of patients whose illnesses or injuries present a significant danger to life, limb, or organ function and encompasses a wide array of diseases and health issues including respiratory failure, shock, severe infection, traumatic injury, burns, neurological emergencies, and multi-system organ failure. The care provided in the intensive care unit (ICU) is highly specialized and complex due to the extreme severity of illness of its patient population, often involving multiple disease processes in different organ systems at the same time. Each year, five million Americans are admitted into adult medical, surgical, pediatric, or neo-natal ICUsⁱ. Providers of critical care require specialized training because the care delivered in the ICU is technology-intensive and the outcomes have life or death consequences. The high resource usage inherent in the ICU often makes care delivery costly.

The Roundtable strongly believes that if we are to truly improve the health of Americans and reduce the economic burden of disease and illness, it is crucial that continued investments be made in NIH-supported research. The basic scientific research that occurs at NIH can provide the foundation for the discovery, development and delivery of new cures and treatments for critically ill patients, and as such, we were very encouraged by the Committee's focus on the role of NIH throughout the first 21st Century Cures event and white paper.

The Roundtable believes that one way to foster progress toward advances in treatments, diagnostics and cures is to improve the coordination of research.

While the critical care community has long been proactive in disseminating new knowledge regarding the pathophysiology and effective treatment of critical illness, we, as a nation, have had disproportionately little focus on critical care research. The U.S. still lags behind other countries in establishing and supporting trial networks for the discovery of new therapies for critically ill patients. Further, a recent study published in the *Journal of Critical Care Medicine* found that despite the fact that cancer care and critical care place similar economic burdens on the U.S., "proportionally 3.1-11.4 times more federal research money was spent on cancer care than on critical care research."ⁱⁱ

The unsurprising result is that relatively few breakthroughs have occurred in critical care medicine in decades compared to other areas of medicine. This fact was recently highlighted in an editorial in the *New England Journal of Medicine* which noted that in 2013 critical care practitioners faced many of the same problems faced by practitioners when the field of critical care was first defined in the 1950s. We can and should do better for patients with critical illnesses.

Clinical advancements that lead to improved outcomes are dependent on a robust research infrastructure that produces new insights and drives innovation. One barrier towards this progress in critical care is likely due to the multidisciplinary nature of the field, resulting in a scattering of critical care related projects throughout the NIH's 27 institutes and across the federal government with very little coordination among the varying entities and researchers.

The Roundtable believes that a Critical Care Coordinating Council within the NIH would help to facilitate information sharing amongst the various Institutes, which would serve to both identify critical care research gaps where resources could be more appropriately allocated, as well as identify duplicative projects. Such a Coordinating Council would foster collaboration between the Institutes and strengthen partnerships between the NIH and public and private entities to expand cross-cutting critical care research without costing the Federal government additional money.

There is precedent for this type of entity. The NIH recently acknowledged the efficiencies that can come from increased coordination by establishing an Office of Emergency Care Research, which is intended to serve as hub for basic, clinical and translational emergency care research and training across NIH. Like emergency medicine, critical care clinicians treat patients across the lifespan who are often facing multiple acute and chronic illnesses and research into this type of medicine does not fit neatly to a specific Institute. Given the impact of critical care

medicine on the nation, the Roundtable believes that a Coordinating Council is necessary to ensure our research dollars are utilized most effectively and yield the greatest result.

The Food and Drug Administration (FDA) also plays a role in supporting innovation in the ICU. As noted earlier, relatively few breakthroughs have occurred in critical care medicine in decades compared to other areas of medicine and FDA's current regulatory processes may play a role in the current pace of innovation. Critical care patients often face myriad challenges and designing trials for treatments to be used in this population can be difficult given the often unpredictable nature of simultaneously occurring acute and chronic illnesses that affect multiple bodily systems. The Roundtable looks forward to working with the Committee to identify policy barriers and opportunities at the FDA to accelerate the pace of discovery and innovation in critical care medicine.

With the aging of the baby boomer generation and in the wake of recent health threats, now more than ever it is essential that we advance our scientific research in critical care medicine to ensure that America has a robust critical care infrastructure to appropriately care for seriously ill patients in the future. The Roundtable on Critical Care Policy strongly believes that investments made in medical research—and in particular, research aimed at the critically ill and injured—will not only improve health outcomes and maintain U.S. leadership in biomedical research, but will also result in significant overall savings to the health care system. We thank you for your consideration.

ⁱ Society of Critical Care Medicine. Critical care statistics in the United States.
<http://www.sccm.org/AboutSCCM/Public%20Relations/Pages/Statistics.aspx>

ⁱⁱ Coopersmith CM, Wunsch H, et al. "A comparison of critical care research funding and the financial burden of critical care illness in the United States." *Critical Care Medicine* 40 no.4 (2012)

Response to 21st Century Cures 1st White Paper: Kevin Conroy, CEO of Exact Sciences

We applaud the efforts of the Cures Project on the Energy and Commerce Committee. It is a remarkable bi-partisan effort by the Committee to maintain and enhance American leadership in the discovery, development, and delivery of new cures and the prevention of disease.

Exact Sciences is dedicated to the early detection of colorectal cancer which kills 50,000 Americans per year and is the second leading cause of cancer death among men and women. We are hopeful that Cologuard, the non-invasive molecular diagnostic test we have developed will lead, if the test is widely adopted, to an increase in screening and a reduction in colon cancer incidence and deaths.

We note that the Committee is focused on the very appropriate circle of discovery, development, and delivery. At this juncture we are focused on delivery of the test to the patients who could benefit from it.

Delivery means getting the discovered and developed preventative measures to the public through both our public and private insurers. Historically there have been several processes that slow down the delivery phase that we hope the Committee will review.

Under current practice there has been a 2-3 year delay between efficacy and safety determination by the FDA and a National Coverage Decision by CMS. With great leadership from Jeffrey E. Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, and Tamara Syrek Jensen, Acting Director, Coverage and Analysis Group, Center for Clinical Standards and Quality, CMS, the two agencies implemented a "parallel review process" that has permitted the efficacy and safety review at FDA to occur more or less in tandem with CMS National Coverage Decision (NCD).

The first invited applicant under this parallel review process is Exact Sciences, In March the *New England Journal of Medicine* published data from our more than 10,000 patient clinical study which demonstrated that the test, known as Cologuard detects 92% of cancer and 42% of all precancerous polyps.

We want the Committee to know that the two agencies have worked well together and with the company. In fact at the conclusion of our FDA panel Dr. Gutierrez from the FDA said:

The Sponsor did something here that is unusual, and I'm going to spend a couple minutes to just describe it because I do think it's important. The Sponsor decided to actually involve both the FDA and CMS, and with the help of the FDA and CMS, they designed a study that really is instrumental in many ways. So the fact that the Sponsor was willing to go the extra step and have a joint review, essentially, from FDA and the CMS is really telling. So I really would like to commend the Sponsor for that. I would like to thank CMS, who got involved early with us and helped design the studies, helped review the data. I really do think that this cooperation was, at least in this case, really fruitful and we learned a lot, and I believe the CMS also learned a lot of how we do business.

This parallel review process should be encouraged and fostered by the two agencies which both currently support the parallel review process.

The parallel review program is an example of government working to spur innovation and help create good paying jobs for scientists, engineers and medical professionals.

We urge that the committee examine ways to strengthen the parallel review program to help make the regulatory process more streamlined so that innovative medical improvements can get to market faster. Doing so will improve both the American healthcare system, as well as our competitive position in the global economy.

Recommendations for 21st Century Cures initiative

We would like to offer the below recommendations to the House Energy and Commerce Committee in regard to the 21st Century Cures initiative:

- The top areas for medical innovation currently are genetics, health information technology and medical devices. As consumers are more directly involved in their own health care, innovation in these areas should consider that patients are becoming more interested in preventative medicine that is personalized and easily accessible.
- National Institutes of Health grants for research have become more difficult for academic centers to obtain. We believe that streamlining of funding by the federal government will support development of new medical technology.
- A great deal of funding had recently come from large pharmaceutical and medical device companies; however, this has decreased in recent years due to a number of factors. The medical device excise tax, enacted as part of the Affordable Care Act, is one of the factors making it more difficult for device manufacturers to support these efforts.
- There are significant costs associated with bringing an idea to market, and the process often takes longer than it should. We support a fast tracked approval process by the Food and Drug Administration (FDA) which also ensures that the patient understands any risk associated with the approved product.
- While the FDA plays an important regulatory role, many of its approval processes are outdated and unpredictable. This is discouraging funding from venture capitalists, and has resulted in decreased funding from other private investors. By standardizing processes, and eliminating uncertain timelines and requirements, the FDA can accelerate approval of medical innovations.
- The private sector is effective at distributing new medical technology, and hospitals and professional societies are effective at evaluating new technology in terms of costs and outcomes. Collaboration among these groups should be encouraged to support the evaluation and distribution of new medical technology.

Academy of Radiology Research

Thank you for the opportunity to provide input to the Committee's thoughtful and transparent process towards a Cures Agenda.

In April of 2014, Committee staff met with members of the imaging and bioengineering research community (convened by the Academy of Radiology Research, guests included Richard Ehman, MD [Mayo Clinic], Richard Frank, MD, PhD [CMO, Siemens], and Mike Harsh, PhD [CTO, GE Healthcare]). In the meeting, attendees emphasized that efforts towards therapeutics development/validation be coupled with the co-development of advanced diagnostic capabilities in order to inform earlier detection, decrease systemic waste and reduce risk to patients. Below are our community's ideas on how the Committee may help achieve these shared goals.

1.) Increase Emphasis on Technology Innovation at NIH

Powerful and advanced technologies have provided the foundation for some of the most significant medical innovations and economic benefits of the last decade.

- Bioengineering, biomedical imaging, and information technologies stand at the crossroads of medicine and technology, the integration of which will shape the clinical landscape for the next century by informing personalized care plans, speeding the translation of effective treatments, and decreasing patient risk.
- Newly analyzed patent data also indicates that NIBIB produces an extremely high rate of jobs-promoting innovations that support one of our country's strongest export industries.

Potential Legislative Strategies

- **Accelerate basic technology development by authorizing the adjustment of the NIH portfolio** to optimize federal return on investment from these areas of research.
 - Because NIH as a whole produces 100-120 new patents per year, even a minor policy shift that would allocate \$200m additional funding to patent hubs like NIBIB (which produces 20-24 patents per year per every \$100m) could *increase the patent output of NIH by 40% per year, and up to 50,000 high-wage jobs over a 10-year period.*
- **Novel funding mechanisms could also be explored, such as repurposing the current USPTO Reserve Fund to the "USPTO Innovation Re-Investment Fund"** – a program that would use PTO annual surpluses (est. \$200m in FY15) to re-invest in the federally-supported R&D programs that generate the most innovations for public funding. This would provide for a germane offset to help replenish the "seed corn" of basic discovery that fuels our innovation economy. OSTP or Commerce would be charged with developing metrics that best measure innovation and tech transfer (such as patents, licensing revenue, etc. – similar to the current language in section 421 of the FIRST Act), and provide a framework for transferring a prescribed level of funding to agencies and programs that meet such metrics. This could be paired with a directive that agency Directors provide 1:1 matching funds in the following year's budget to help ensure that agency leaders are beginning to use innovation metrics as part of the budget process, and that the dollars supplement – not supplant – existing budget authority.

2.) Leverage the Power of Advanced Diagnostic Technologies for Individualized Medicine and Accelerating Cures

The imaging research community agrees with the testimony from the Biotechnology Industry Organization (BIO) at the Committee's May 21 hearing – specifically in regard to their

membership survey results on most pressing research needs. Of the top 5 research needs, the imaging research community would be central to the top two: a.) biomarkers for predicting therapeutic response and b.) novel clinical trials designs.

Potential Legislative Strategies

- **Encourage increased programmatic efforts at NCATS focused on diagnostic biomarkers that are individualized, predictive, and high value.** Ask that NCATS collaborate with the NCI Cancer Imaging Program (CIP) for successful current initiatives that streamline the research and development process for biomarkers, such as novel programs aimed at toxicology testing/GMP program for promising radiotracers (Paula Jacobs, PhD of the NCI CIP could talk more about this specific program aimed at bridging the gap from bench research to FDA approval of imaging agents).
- **Encourage greater use of pragmatic randomized control trials at NIH, such as the new NHLBI RFA this year.** Because these randomized control trials represent the highest level of evidence, and FDA is increasingly becoming risk averse, these types of trials are becoming mandatory for FDA approval. However, because they are sometimes “mundane” and not “innovative,” they typically are not funded via the normal peer review process at NIH – putting this type of research in the “valley of death”. Therefore, policymakers may want to consider two approaches: encourage FDA to use other evidentiary standards in approving agents such as imaging biomarkers (see below), or encourage NIH to provide more targeted RFAs (like the NHLBI one above) to ensure dedicated funding for this now-necessary activity.
- **Encourage NIST to expand its work in generating standards across different imaging vendors,** which would help meet FDA desire for reduced variability/subjectivity for imaging biomarkers. This also doesn’t fall into typical research or discovery that is funded by NIH. Rather, it’s the increasingly important “engineering” of diagnostic agents – after discovery – that is becoming required by FDA more and more in order to gain approval.
- **Request IOM to report on** a.) the use of diagnostic technologies and biomarkers to reduce the cost of clinical trials; b.) the potential to improve healthcare and decrease costs by using advanced diagnostic technologies/biomarkers in a proactive, targeted, and definitive manner to dramatically reduce diagnostic uncertainty and patient risk; c.) and to estimate the healthcare burden and aggregate costs of uncertainty and diagnostic error.

3.) Address the Discrepancy between the Accelerating Rate of Technological Innovation and a More Rigid Regulatory System for Assessment and Clinical Introduction

Mismatch between the pace of advances in innovative technologies and the growing time required to satisfy cumbersome regulatory requirements threatens patient access to the benefits of publicly-supported innovation.

Potential Legislative Strategies

- **A sense of the Congress that FDA should restructure the risk profile for qualified biotechnologies** by streamlining regulatory approval to allow for smart and flexible clinical implementation during evidence acquisition phase
 - FDA now routinely requires outcomes research (see bullet above about NIH pragmatic clinical trials) for imaging biomarkers/diagnostics. This doesn’t reflect the significantly decreased risk to the patient (used only a handful of times in the patient for diagnosis, monitoring or staging – as opposed to a once-daily drug for 10-30 years), and significantly different business model for these

products (blockbuster drugs can reimburse pharmaceutical companies for significant R&D and FDA validation costs, while imaging agents are used less frequently and do not support the heightened cost of validation/approval).

- **Direct FDA to exercise its existing statutory authority allowing for more streamlined approval for diagnostic/imaging biomarkers.** FDA has approved guidance (2004) for validating imaging agents, and lists 4 levels of evidence that could be satisfied. However, FDA typically requires the most difficult and costly level of evidence (outcomes) for imaging biomarkers. FDA should use other approved levels of evidence (e.g., disease detection; pathological assessment [i.e., did the imaging agent provide the information promised?]) that are more germane to the critical informational role of biomarkers (screening, diagnosis, monitoring), and not outcomes evidence which is more relevant to validating the drugs that treat disease (which should require outcomes data [i.e., did the drug work or not?]).
- **Clinical trial reforms:** Speed the process of drug/device testing, including the development of a global platform of linked patient registries, longitudinal trials and standing 'trial-ready' cohorts of well-characterized patient populations ready, willing and able to participate in single or combination drug trails.
- **Direct CMMI pilot projects** that explore delivery models that reward early and accurate diagnosis within a value-based model



Accelerate Cure/Treatments for Alzheimer's Disease

Advisory Council

May 30, 2014

Alliance for Aging Research

The Honorable Fred Upton
Chairman

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

Alzheimer's Foundation of America

U.S. House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

American Society on Aging

National Alliance for Caregiving

RE: Comments on [21st Century Cures: A Call to Action](#) White Paper

National Association of Area Agencies on Aging

Dear Chairman Upton and Representative DeGette,

National Consumers League

The coalition to [Accelerate Cure/Treatments for Alzheimer's Disease \(ACT-AD\)](#) is comprised of more than 50 national organizations representing patients, caregivers, researchers, health professionals, and other health advocates. For the past nine years we have supported efforts to expedite the development, review, and approval of transformational therapies for Alzheimer's disease (AD). On behalf of ACT-AD, we would like to thank you for your leadership in announcing the 21st Century Cures Initiative. We understand all too well that many of the discoveries made today will not provide relief in time to reach the millions Americans expected to suffer from the devastating effects of Alzheimer's in the next decade. Thank you for your desire to provide hope to these patients and their families by endeavoring to shorten the time it takes to bring new treatments to market. ACT-AD appreciates the opportunity to comment on the Committee's first white paper about what could improve treatment discovery, development and delivery for Alzheimer's disease.

Research!America

Society for Women's Health Research

As you are well aware, more than 5 million Americans currently live with Alzheimer's disease. By the middle of this century that number is expected to double. Without more meaningful treatment options that allow for improved quality of life for those with the disease or interventions that halt, delay or reverse progression of AD in its earliest stages, the human and economic burdens associated with this disease will continue to advance at unsustainable rates. In recent years several late-phase therapeutic development programs for Alzheimer's disease were discontinued due to marginal or negative results. In response to challenges faced in these programs, the U.S. Food and Drug Administration (FDA) became a more active partner in the development process for Alzheimer's disease by routinely participating in [meetings and conferences](#) with patient advocates, the scientific community, and industry focused on improving AD clinical trials and issuing [draft guidance](#) for industry further clarifying requirements for testing early-stage Alzheimer's treatments. The National Institutes of Health (NIH) has also recently elevated the importance of Alzheimer's disease research by advancing [three clinical trials](#) targeting earlier intervention in the disease course and specific gene mutations that predispose a person to develop Alzheimer's disease. By forming the Accelerating Medicines Partnership, NIH will be able to leverage resources and data from the public and private sectors to make more rapid advances in identifying Alzheimer's biomarkers

that predict a treatment outcomes. We applaud the FDA and NIH for making these commitments that prioritize Alzheimer's disease based solely on the societal threats this disease poses despite a lack of commensurate resources to offset their involvement in these research and regulatory activities.

Several years ago, we and our colleagues in the advocacy community called on Congress to create the National Center for Advancing Translational Sciences (NCATS) at NIH because of its unique ability to aid in the translation of basic scientific discoveries into treatments for diseases like Alzheimer's. One approach taken by NCATS is drug repurposing under its "Discovering New Therapeutic Uses for Existing Molecules" program. Repurposing has had very promising results in treating difficult diseases including HIV/AIDS and certain cancers. We hope for similar success in repurposing drugs for the treatment of Alzheimer's disease. One NCATS project was started in 2013 to use a repurposed drug to block activity of a certain Alzheimer's-linked protein in mice. The results of this study have not been released and the effects of this treatment in humans are not yet known. However, this week NCATS put out a call for applications to "New Therapeutic Uses" program. This round of funding provides the added incentive of an additional year of support for researchers looking to study available drugs for pediatric indications. Given that the study of drugs for age-related disease like Alzheimer's in geriatric populations (of mice and humans) pose many complexities as do trials in pediatric populations, and drug repurposing was one of six major themes identified by the NIH at the Alzheimer's disease research summit it held in 2012, we would ask that the Committee consider making a recommendation that Alzheimer's disease applications to the "New Therapeutic Uses" program be considered for added incentives in future solicitations put out by NCATS.

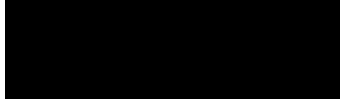
In 2012 and 2013, at the suggestion of the former head of the Neurological Products Division at FDA, ACT-AD co-convoked two pivotal meetings looking at the potential for a combination approach to treating Alzheimer's disease. Participants at the meetings discussed the possible benefits and challenges associated with combining treatments for AD, from basic mechanisms through regulatory approval. Advocates, industry, the scientific community, and regulators have coalesced around AD combination therapy in theory but it is slow to take root in reality. A lack of research into what Alzheimer's targets should be pursued in combination, difficulties in navigating a company's rights to different treatments that would make up a drug combination, and issues of antitrust linked to drug pricing are barriers to moving combination therapy to the forefront of AD drug development. We believe combination therapy should be more explicitly considered as part of research, regulatory and reimbursement strategy discussions related to Alzheimer's. The 21st Century Cures Initiative could be a vehicle for proposing mechanisms to remove these barriers. Without easing these restrictions, we stand to lose many years in capitalizing on an opportunity that was crucial to the success in turning lethal diseases like HIV/AIDS, forms of cancer and tuberculosis into treatable conditions.

Lastly, we welcomed the FDA's draft guidance on early Alzheimer's drug development in 2013 because it expressed the conditions under which they would consider the use of Accelerated Approval for an AD treatment, however the guidance also included a requirement for some patients that fall in the early stages of the disease to improve their cognition and function when on a drug in a clinical trial. This is problematic because at least one study has shown that cognitive decline precedes functional symptoms. Looking ahead to the future, there may be sensitive enough instruments developed to measure both cognition in function in these early patients but at this point emerging research shows that using what is available today these early and mild patients are not able to demonstrate functional improvement with existing ways of measuring function in current trials. In

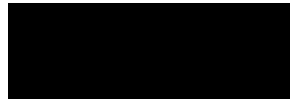
situations like these, we would ask that the FDA retain the ability to remain flexible to alternative approaches in deciding whether or not an improvement in cognition alone is meaningful enough for patients to warrant approval. Any changes to the regulatory process proposed by the Committee as part of this 21st Century Cures Initiative should be sensitive to evolving challenges of ongoing trials and not unintentionally disruptive to a therapeutic area.

Thank you for your careful consideration of the views expressed above. We hope the Committee will contemplate provisions that advance these important and promising areas for improving Alzheimer's drug development when it moves to legislative action. Please feel free to contact Cynthia Bens at [REDACTED] with any questions.

Sincerely,



Daniel Perry
Chairman



Cynthia Bens
Vice President, Public Policy

The Advanced Medical Technology Association's (AdvaMed) Comments on
21st Century Cures: A Call to Action
Submitted to the House Energy and Commerce Committee
June 1, 2014

AdvaMed enthusiastically supports the call to action issued by Chairman Upton, Representative DeGette, and the Energy and Commerce Committee. The medical technology industry is central to the development of medical devices and diagnostics that will provide the life-saving and life-enhancing treatments of the future. But the innovation ecosystem that supports our industry is severely stressed. Policy improvements are essential if America is to retain its world leadership and the potential for medical progress in this century of the life sciences is to be fulfilled. The opportunity for better treatments and cures is immense, but patients will only reap the benefits if the ecosystem is strengthened. Failure to act will mean lost lives, unnecessary suffering, reduced job formation, and diminished economic growth.

Background on the medical technology industry

The medical technology industry is composed of companies that develop and manufacture medical devices and diagnostics. These products are diverse, running the gamut from tongue depressors to the most complicated molecular diagnostic tests, advanced imaging machines, and cardiac implants.

Structurally, small firms are a key part of the medical technology industry. A 2007 study by the U.S. International Trade Commission (USITC) found a total of 7,000 medical technology firms in the U.S.¹ The U.S. Department of Commerce estimated that 62% of medical technology firms had fewer than 20 employees and only 2% had more than 500.² Even large companies in the medical technology space tend to be smaller than large companies in many other sectors. There are only four pure device and diagnostic companies in the Fortune 500 and none in the Fortune 100.

Small firms, often funded by venture capital, are particularly critical to the future of U.S. scientific and technology leadership because they are the source of a disproportionate number of the breakthrough technologies that drive medical practice and industry growth.³

Whether created by large or small firms, medical technologies are characterized by a rapid innovation cycle. The typical medical device is replaced by an improved version every 18-24 months.

To fuel innovation, the medical device industry is research intensive. U.S. medical technology firms spend over twice the U.S. average on research and development. Medical device companies specializing in the most complex and technologically advanced products devote upward of 20% of revenue to R&D.⁴

In part because of this rapid innovation cycle, the medical technology industry is highly competitive. A study of medical device prices from 1989 to 2009 found that they increased, on average, only one-fifth as fast as other medical prices and less than one-half as fast as the regular CPI. Because the highly competitive market kept prices low, medical devices and diagnostics accounted for a relatively constant 6% of national health expenditures throughout the 20-year period despite a flood of new products that profoundly changed medical practice.⁵

The U.S. medical technology industry is a very dynamic part of the U.S. economy and a source of economic growth and good jobs. The industry employs more than 420,000 people in the U.S. It generates an additional four jobs in suppliers, component manufacturers, and other companies providing services to the industry and its employees, for every direct job—for a total of more than two million jobs nationwide.⁶

The jobs the medical technology industry provides are good jobs. The average medical technology worker enjoys wages that are almost 40% higher than average pay for the economy as a whole and 22% higher even than the average for manufacturing wages.⁷

The products created by the medical technology industry are an essential part of modern medical practice, and development of new medical technology has been one of the main engines of medical progress.

In no small measure as the result of the diagnostics, treatments, and medical tools developed by the medical technology industry, the health advances of recent years have been breathtaking. Between 1980 and 2010, medical advancements helped add five years to U.S. life expectancy.⁸ Fatalities from heart disease were cut by 57 percent;⁹ deaths from stroke were reduced by 59 percent;¹⁰ mortality from breast cancer was cut by 31 percent;¹¹ and disability rates declined by 25 percent.¹² Moreover, the pace of positive change has quickened. In the most recent decade, between 2000 and 2010, life expectancy increased by nearly two years.¹³ Fatalities from heart disease were cut by 30 percent;¹⁴ deaths from stroke were reduced by 36 percent;¹⁵ and mortality from breast cancer was cut by 18 percent.¹⁶

The dramatic improvements in health have gone beyond reduced mortality to improved quality of life. The proportion of the elderly with a functional limitation has declined and the years of disability-free life expectancy have increased.¹⁷ To cite just one example of technology's impact, patients who received total hip or total knee replacements typically

transitioned away from disability within one year. Their risk of dying was cut in half and their risk of a new diagnosis of heart failure or depression was significantly reduced.¹⁸

While the gains in health over the last thirty years have been impressive, and those of the last ten years even more striking, past progress pales compared to future opportunities. In this century of the life sciences, technological advances driven by fundamental advances in knowledge of human biology and continued progress in computing, communications, materials science, physics and engineering can be expected to fuel creation of new and better medical technology products—if there is a sound innovation ecosystem supporting not only continued scientific progress but the translation of scientific advances into better health

The innovation ecosystem under stress

As the committee points out, “The discovery, development, and delivery process is a cycle . . . The country that fully embraces the entirety of this cycle will be the innovation leader for the 21st century.” For the nation’s medical technology industry, every part of this cycle—the innovation ecosystem—is under stress.

The danger signs include:

- Reduced investment. Venture capital flowing to the medical device sector is both an essential generator of future progress and an index of the attractiveness of investing in the development of new treatments and cures. Many of the true breakthrough therapies and diagnostics in the medical technology industry flow from venture funded start-ups. Venture investment in medical technology declined by one-third between 2007 and 2012.¹⁹ It declined an additional 17 percent in 2013, and did not increase significantly in the first quarter of 2014.²⁰ Even more ominous is the decline in investment for start-up companies at the earliest stage—the seed corn for the next generation of treatments and cures. First time funding for medical technology start-ups dropped by three-quarters between 2007 and 2012. And the fraying of the ecosystem is nowhere better illustrated than by the number of venture firms that have given up on medical technology altogether. The number of venture capital firms investing in medical technology declined from 39 in 2007 to just 11 today.²¹
- Movement of clinical trials and first product introduction out of the United States. For more complex products, the new normal is to conduct the first clinical trials and product introductions outside the U.S. Often, patients in other nations get the second or even third version of a novel treatment or diagnostic while patients in the U.S. are still waiting to get the first version. Among other factors, the decisions to introduce abroad first are driven by the higher cost and time involved in conducting clinical trials in the U.S.; delays and

inconsistencies in FDA review, including review of proposals for Investigational Device Exemptions (IDEs); and, increasingly, uncertainties about coverage and payment.

- Increasing difficulty in achieving coverage by public and private insurers for new medical devices and diagnostics. The openness of the U.S. medical system to new treatments and diagnostics has been a major strength in stimulating U.S. leadership in development of new products and rapid patient access to improved care. Public and private insurers, however, are raising the evidentiary threshold for coverage. A study by researchers from Tufts University found that the probability of a therapy that is considered for Medicare national coverage receiving a favorable decision dropped by more than 60% between 1999 and 2007.²² When coverage was granted, it was more limited than the FDA approved indications in 40 percent of the cases. A survey of insurers reported that large proportions said that they had raised their requirements for coverage in the last three years and a larger proportion expected to raise requirements further over the next three years.²³ New payment methods such as ACOs and bundling and other provider risk-sharing programs spreading rapidly in both the public and private sector can have the effect of penalizing providers who adopt new, more costly treatments, even if they represent therapeutic improvements.

Start-up companies are reporting that the one of first questions that investors now ask is often about the prospects for coverage and payment, while the previous focus was almost exclusively on the FDA.

The solution is not to move back from appropriate incentives to provide high value care or to suggest that products that do not offer therapeutic benefits should be covered; rather it is to make the public policy changes necessary to assure that the new emphasis on cost does not result in the unintended and unwanted consequence of undermining development and adoption of new and better treatments.

- Declining U.S. competitiveness. As the committee notes, other countries are anxious to wrest leadership from the U.S. in biomedical research and in the life sciences industries. The U.S. medical technology industry has been the unchallenged world leader for many years. We still lead, but our continued leadership is clearly threatened. A study in 2011 by Price Waterhouse Coopers showed U.S. leadership on each of five pillars of medical device innovation to be eroding.²⁴

AdvaMed preliminary recommendations for consideration by the Committee

FDA

The user fee agreement and the accompanying bipartisan legislation developed by this Committee enacted in 2012 has set the FDA on an improved course, and the commitment from the leadership of the device center to make the U.S. the most attractive place in the world to introduce new products is heartening, as are recent improvements in FDA performance on such measures as increased clearance and approval rates and PMA review times. However, while performance is now better in some important respects than the nadir reached in 2010, it is still well below both the standards of the recent past and what is achievable. As noted above, lack of timeliness and consistency in FDA review has been a major reason for movement of clinical trials and first product introduction abroad and the drying up of venture investment. As part of the 21st Century Cures initiative, it will be important to analyze all the reasons for these trends and find ways to reverse them.

Keys to further progress include:

- Continued implementation of the user fee agreement, with the goal of reaching and exceeding the MDUFA performance goals. In this connection, continuing Committee oversight of the FDA's implementation of the user fee agreement, FDASIA, and FDA activity generally is critical to continued success.
- Sustained focus on management improvement and reviewer training to achieve increased timeliness and consistency of review. Successful implementation of the recommendations of the independent management study mandated by the user fee agreement will be especially important.
- Consideration of ways to reduce the time and cost of clinical trials, including possible methods of streamlining IRB approval, reducing unnecessary preclinical trial data, and improving the IDE process.
- Continued development and expansion of the reciprocal inspection program to reduce cost of U.S. manufacturing, while maintaining rigorous standards.
- Improvement of procedures for evaluation and approval of combination devices. With the progress of technology, devices that combine both device and drug elements to provide effective treatments are expected to become more common and even more important. FDA's current procedures result in inappropriately long reviews for these products and difficulty in coordinating work between the FDA centers involved.
- Increased use of international consensus standards in product review. Certification to international standards is allowed for elements of PMA and 510(k) review, and can be the sole basis for approval of special 510(k) products. Expanded use of international

consensus standards could speed review and expedite approval in both U.S. and international jurisdictions.

- In the diagnostic space:
 - Rapid implementation of a transitional approach to diagnostics approval, as specified in the user fee agreement. Diagnostics, especially molecular diagnostics, represent in many ways the future of medicine. They are key to personalized medicine. They assist in rapid and precise diagnosis, in targeting existing treatments, and in pointing the way to the development of new treatments. A sound regulatory system is key to maintaining the investment in development of these often revolutionary new products, and the transitional approach described in the user fee agreement is an important step toward speeding development and availability of these new medical tools.
 - Improvement in the CLIA Waiver by Application Process. CLIA waivers are needed to allow diagnostic tests at the bedside or in the doctor's office, rather than requiring that a specimen be drawn and sent to a laboratory. Sophisticated on-the-spot testing is increasingly technologically feasible. Where medically appropriate, rapid turnaround of test results can reduce costs and improve care—but to make such tests available and to encourage investment in their development, FDA needs to improve its process for waiving CLIA requirements.

Payment and Coverage

As noted above, increased difficulty in achieving insurance coverage by public and private payers and financial incentives that discourage providers from adopting more costly treatments, even if the treatments are clinically superior, are emerging as substantial impediments to investment in and development of new treatments and cures and to their diffusion once approved by the FDA. Ironically, even new treatments that potentially lower costs can be disadvantaged if the savings occur over the long term while the costs appear immediately. Because their covered population turns over fairly rapidly, insurance companies tend to be less interested in cost savings that accrue over a period of years and more concerned about up-front costs. In risk-sharing payment arrangements, under which providers are rewarded or penalized for the costs they incur, the calculation of costs is virtually never longer than a year and is usually shorter, e.g., for an episode of hospitalization. And, of course, savings that accrue to individuals and society outside the health care system—through reduced disability, increased labor force participation, and reduced burdens on caregivers—are never factored into these calculations.

AdvaMed recommends that the Committee consider a number of changes to the Medicare program. These changes would help support development of new treatment and cures without undercutting the bipartisan goal of reorienting the program to do more to reward reduced expenditure growth and higher quality.

- Automatic Medicare coverage of clinical trials approved or sponsored by FDA, NIH, or other government agencies. The requirement that Medicare cover certain costs associated with clinical trials was never intended to be based on whether the information gathered would support Medicare coverage. Instead, it was intended to support the general research endeavor to develop new treatments and cures and to provide the opportunity for enrollees to participate in trials that might benefit them. Most trials are ultimately approved for coverage by Medicare, but the process for gaining approval can be time-consuming and costly. The new centralized approval requirement that Medicare is establishing could turn into an unnecessary bottleneck for launching trials. Separate Medicare review of the study design and protocol of a clinical trial should not be necessary if the trial has already been scrutinized to assure that it is scientifically sound and has appropriate protection for participants by specialized reviewers at the NIH, FDA, or another government agency.
- Establish a requirement that Medicare, in making national coverage decisions, should take into account patient views of what is “reasonable and necessary,” just as FDA, at the urging of this Committee, is implementing a requirement to take into account patient views of risk and benefit in making approval decisions. While CMS includes some patient representatives on the MedCAC advisory committee, this has not provided a systematic or adequate method of assessing patient views and giving them appropriate weight. The proposed requirement would help assure that coverage decisions take adequate account of the views and needs of Medicare beneficiaries rather than being driven by a potentially overly narrow perspective.
- Establish a legislative mission statement for Medicare that includes promoting the development and adoption of better treatments and cures for Medicare beneficiaries, analogous to the addition to the FDA mission statement approved by this Committee in 1997, providing for “advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable.” While the President’s executive order 13563 stated that “each agency shall also seek to identify, as appropriate, means to achieve regulatory goals that are designed to promote innovation,” it is not clear that CMS sees innovation in the development of new treatments and cures as part of its mission, despite the very strong interest of current and future elderly and disabled Americans in the most rapid medical progress possible.

- Assure adequate oversight of CMS' implementation of the historic diagnostics payment reform provisions in the recently-enacted Protecting Access to Medicare Act (H.R. 4302; Pub.L. 113–93) to ensure an effective transition to the new market-based diagnostics reimbursement system, adherence to new transparency requirements, and effective adoption of the new diagnostics coding requirements. In view of the large and importance role of diagnostics in guiding treatment decisions and the rapid expansion in the number and precision of diagnostic tests, especially molecular diagnostic tests, Medicare should also promote expanded quality measures for use of diagnostics.

As noted above, molecular diagnostics represent in many ways the future of medicine. It is critical that the Medicare payment system support continued investment in this tremendously important area of medicine.

- Direct CMS to provide transparency in monitoring the quality of care provided under Medicare payment methodologies that involve provider risk-sharing and assure that such monitoring will include mechanisms to assure that patients' access to medically appropriate treatments is not limited. New payment methodologies such as Accountable Care Organizations and bundled payments are designed to create incentives for quality and cost reduction. At this point, however, the incentives for cost reduction are strong, while the measures of quality are relatively limited. There are many ways to reduce costs that do not involve stinting on care—better management of chronic disease across the continuum of acute and post acute settings, more effective prevention, higher quality care that ultimately reduces the burden of disease, more efficient management of the processes of care that would reduce inpatient admissions, elimination of unnecessary care—but there is also the possibility that the new incentives could lead to stinting on care and denying patients access to appropriate treatments based on cost, including new technologies. If this occurs, it is not only a problem for individual patients but could reduce incentives for development of new treatments for the whole population. The Medicare program has made a commitment to monitoring the care received by beneficiaries to assure that stinting does not occur; the methods used in monitoring should be transparent so that gaps can be identified and addressed.
- Direct Medicare to provide transparency on the amount of payments received by individual providers under risk-sharing programs, as well as the methodology used by entities participating in such programs to establish reimbursement bonuses and penalties. Such transparency would be another important and appropriate tool to guard against stinting on care.
- Direct Medicare to establish a time limited reimbursement add-on or pass through for the additional cost of new technologies in ACO or similar programs if these new

technologies offer the potential for significant clinical improvements and would add to costs during the payment period. The goal would be to assure that the incentives in the new systems are neutral and neither encourage nor discourage adoption of treatments that will improve the health of beneficiaries, so that providers can make the critical decision to be early adopters of new technology based solely on clinical considerations. The process would be analogous to the inpatient new technology add-on payment or the outpatient transitional pass-through payment that CMS now applies to hospital payments. Congress established these programs because it recognized that the DRG and outpatient payment system provided inappropriate disincentives for hospitals to adopt new technologies. The same disincentives exist in the new provider risk-sharing programs such as ACOs and bundled payments, and a similar remedy should be provided.

- Improved administration of the Coverage with Evidence Development (CED) program. The CED program was originally designed with the desirable goal of providing coverage for promising therapies for which the existing evidence was inadequate to fully meet the reasonable and necessary criteria. During the CED period, evidence would be gathered to either justify regular coverage or decide that the therapy did not meet the standard. In the industry view, CED has frequently been used to unnecessarily limit coverage for therapies. Regulation should stipulate that the purpose of CED is to expand coverage rather than limit coverage. In addition, CED study requirements have sometimes not provided clear endpoints for data collection or standards for determining when a therapy merits full coverage, and have added unnecessary burdens to the post-market requirements already imposed by FDA.
- Streamline the process for assigning billing codes to new technologies. Although receipt of a code is often a prerequisite to coverage and payment, it can take up to 18 months after FDA approves a new technology for a code to be provided—effectively depressing the timeliness of reimbursement and delaying patient access to new treatments and cures.
- Consider additional steps to encourage investment in development of new treatments and their prompt availability to patients under Medicare, including routine coverage for the full FDA labeled indications when coverage is granted, improving the new technology add-on process by establishing less limiting criteria and a payment adjustment closer to the full cost of the new treatment, and using the most timely cost data for assignments of new technologies to DRGs.

Next Steps

AdvaMed is in the process of developing a proposal to encourage development, rapid FDA clearance, and expedited coverage of breakthrough products that have the potential to

transform care for patients facing diseases for which there are no treatment alternatives or for which alternatives are inadequate. We will share this proposal with the Committee as soon as it is completed.

In addition, we will be reviewing the entire innovation ecosystem to see if we can develop additional ideas to share with the Committee.

Conclusion

AdvaMed appreciates the opportunity to work with Chairman Upton, Representative DeGette, and the Energy and Commerce Committee on the 21st Century Cures initiative. On a personal level, all of us know that nothing is more important than good health for ourselves and our families. As Americans, we understand that the economic future of our country will depend in no small measure on our continued leadership in the life sciences. And from a scientific viewpoint, we know that opportunities for rapid advances in the understanding of human biology and the development of life-changing diagnostics, treatments, and cures are breathtaking. But, as this Committee recognizes, our ability to realize the goals implicit in these understandings depends on wise public policies.

Today, the innovation ecosystem is frayed and repair is needed. The 21st Century Cures initiative is an opportunity to make the future a brighter one for every patient and every American.

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May 30, 2014

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

The Honorable Diana DeGette
Ranking Member, House
Energy & Commerce Subcommittee
on Oversight & Investigations
U.S. House of Representatives
Washington, D.C. 20515



Dear Chairman Upton and Congresswoman DeGette:

The American Academy of Dermatology Association (Academy), which represents more than 13,000 dermatologists nationwide, applauds your leadership in seeking stakeholder input on ways the U.S. can facilitate accelerated discovery, development, and delivery of biomedical innovations. Our nation is at a crossroads to maintain its status as the premier leader in biomedical research, at a time when fewer federal dollars are being allocated to the National Institutes of Health and other research agencies. Unfortunately, other nations are poised to surpass us in direct investment in scientific research.

At any given time, 1 in 3 Americans suffers from a skin disease. As dermatologists on the front lines fighting skin cancer, and diagnosing and treating more than 3,000 skin diseases, including infections, immunologic diseases, and genetic disorders, we urge Congress' support for biomedical research that builds on past innovations, fosters momentum in scientific research, and advances medical knowledge. To ensure that the research being supported today yields the breakthroughs of tomorrow, sustained funding is critical to achieving long-term and permanent treatments and cures. In recent year's budget cuts and fiscal pressures have had a direct impact on current and future research projects, potentially limiting our patients' access to life-saving treatments and cures in the future.

The current level of federal investment in medical research is insufficient to yield tomorrow's medical breakthroughs. At its funding peak in 2003, the budget for National Institutes of Health (NIH) represented about 0.24% of the Gross Domestic Product (GDP). However, it has steadily declined since then and now represents less than 0.20% of GDP. When factoring in the rate of inflation, the budgets for the NIH and National Cancer Institute (NCI) are, respectively, 22% and 25% less than what they were ten years ago. Meanwhile, China has committed to increase its investment in basic research by 26% with more than \$300 billion going into in biotechnology over a five year period. This is nearly double what the federal government will invest in the life sciences.

These statistics should give us pause, as federal funding is not aligned with the impact biomedical research has on the U.S. economy. We are also concerned that the long-term effect of these decisions could have a negative impact on U.S. global economic competitiveness in the future. A recent economic analysis concluded that for every federal \$1 invested at NIH, \$2.21 is generated in economic activity. The life sciences support more than 7 million jobs and contribute \$69 billion annually to the GDP. Our nation has a history of public-private partnership in this important area, and the private sector has regularly looked to and built on the

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success of federally funded research, particularly for basic biomedical research, the foundation for biomedical innovation in the private sector. Inadequate funding for medical research has immediate consequences as it has severely impacted NIH's ability to award grant applications. In the early 1960's, NIH had a nearly 60% RO1-equivalent application success rate. Today that rate is about 20% even as the applications are of significantly higher quality. Funding has not kept up with the increased number of trained scientists or with cost-of-living increases. At some NIH institutes, paylines are at historical lows, dropping down to single-digits. This generation of scientists faces a hypercompetitive job market that is increasingly difficult to enter, combined with a lack of long-term job security. In the United States, biomedical research is decreasing in its attractiveness as a career choice and employment prospect, squeezing many of the most brilliant scientific minds into other fields or out of the country. Moreover, the entities that allocate funds to biomedical research require increasingly narrowly tailored research questions, preventing scientists from expanding knowledge and discovering new, unexpected, innovations. Many students and researchers that benefit from world-class American research universities and institutions are starting to take their knowledge to other countries offering biomedical researchers more support and better career prospects. These scientists need to be encouraged that investment in biomedical research is a national priority, and this starts with our government's leadership.

While increasing funding would best serve our nation's research infrastructure, it is also vital that efforts be focused on breaking down outdated and redundant regulatory burdens at the Food and Drug Administration (FDA). The approval pathway is outdated and is no longer safe, effective, and advantageous for tomorrow's medical breakthroughs. Given the advances in knowledge and technology, the regulatory process can evolve while maintaining patient safety. Likewise, the U.S. should have the top experts at the table to weigh in on scientific questions. Unfortunately, conflict-of-interest rules are preventing many of our nation's leading scientists and thinkers from being able to engage in meaningful discourse in their areas of expertise with federal agencies. We must reform the system that excludes scientific experts in the biomedical field away from decision-making that impacts public health.

Burdensome regulations oftentimes work to the detriment of protecting the public health. While incidence rates for some cancers have decreased over the last few decades, rates for melanoma skin cancer have been increasing. Dermatologists treat more than 2.2 million people with skin cancer every year in the U.S. and based on current trends, 9,710 Americans will die from melanoma in 2014. Many of these skin cancers could have been prevented with protection from the sun's rays.

The Committee is well aware that the FDA has not approved a new sunscreen ingredient since the 1990's despite the fact that some of these ingredients time and extent applications (TEA) have been pending for more than 10 years. Consequently, the American public does not have access to some of the more advanced sunscreen products commonly used in other western nations. Simply put, regulatory review and approval may be hindering already developed and tested potentially lifesaving products from entering the market. Federal agencies should have achievable purviews, the tools and frameworks necessary to act efficiently and within a certain timeframe, and be held accountable for such.

If the U.S. is to remain a leader in the field of biomedical innovation, we must provide adequate levels of funding for continued biomedical innovation, simplify processes at the federal level, and encourage new researchers to enter the field. We appreciate your continued leadership on this issue and look forward to working with you on this important initiative. The Academy would like to serve as a resource to you and the Committee as you continue to seek stakeholder input

on these critical issues in the coming months. If you have any questions or if we can provide any additional information, please contact Niva Haynes, the Academy's Manager, Congressional Policy, at [REDACTED]

Sincerely,

[REDACTED]

Brett M. Coldiron, MD, FAAD
President, American Academy of Dermatology Association

**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.

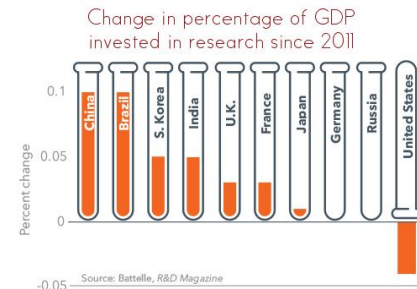
Because we ourselves are working hard to create a sustainable biomedical research enterprise, we are delighted that the U.S. House Energy and Commerce committee is also addressing the critical issues confronting biomedical research today. Biomedical research has a long history of bipartisan support, 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.

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>

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

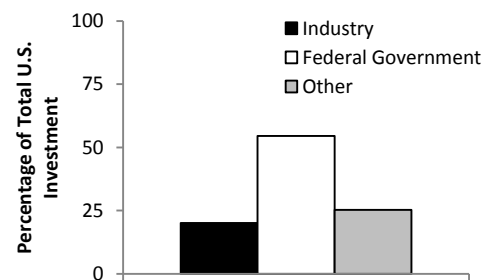
To ensure that the U.S. maintains its leadership role in global research and discovery, the federal government must commit to being the enduring foundational investor in basic biomedical research. Federal investment in basic research is the cornerstone of the entire enterprise. This investment has led 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>

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>

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.



Michael J. Guastella, MS, MBA
Executive Director

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May 30, 2014

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

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

Re: 21st Century Cures: A Call to Action

Dear Chairman Upton and Ranking Member DeGette:

I am writing on behalf of the Council on Radionuclides and Radiopharmaceuticals (CORAR) to comment on the white paper entitled, “21st Century Cures: A Call to Action” released on May 6, 2014. CORAR commends the Committee for this new initiative which is designed to examine and enact changes to the current regulatory and delivery system in order to spur continued investments and innovations in the healthcare sector that may translate into treatments and cures for patients worldwide.

CORAR is an association of companies in the United States and Canada that manufacture radiopharmaceuticals, sealed sources, and radionuclides primarily used in nuclear medicine procedures, and that operate nuclear pharmacies that dispense these products to health care providers for administration to patients.

Benefits of Nuclear Medicine:

Every year, it is projected that approximately 14 million nuclear medicine procedures are conducted in the United States. Within nuclear medicine a number of diagnostic applications exist to diagnose illnesses such as heart disease, lung disease, cancer, brain abnormalities and bone infections. Nuclear medicine is one of the most powerful analytic tools available to physicians and patients today because of its unique ability to provide information on both the function and structure of an organ. In addition to products currently available today, the nuclear medicine industry is committed to developing innovative radiopharmaceuticals to advance patient care. Below are some examples of nuclear medicine in action:



- Radiopharmaceuticals designed to facilitate myocardial perfusion imaging which allows nuclear cardiologists to image the heart, assess patients for the presence and extent of coronary artery disease, and recommend appropriate treatment
- Bone scans using radiopharmaceuticals allow radiologists to detect patients with metastatic cancer six to eighteen months earlier than with X-ray
- Positron Emission Tomography (PET) Imaging of tumor patients with a radioactive glucose analog (FDG) enables radiologists to more accurately stage cancer patients and help oncologists select treatment plans
- Brain Imaging to investigate abnormalities in the brain, such as seizures, memory loss and abnormalities in blood flow can detect the early onset of neurological disorders such as Alzheimer disease
- Radiopharmaceuticals and radioisotopes are used to treat diseases such as Grave's Disease (hyperthyroidism), Non-Hodgkin's Lymphoma (the fifth most common cancer in the United States), prostate cancer, and thyroid cancer.

Nuclear medicine provides many benefits to patients, but the industry is facing challenges as it continues to grow and innovate.

While imaging agent regulatory requirements for safety and efficacy are similar to those of therapeutic drugs, and clinical trial costs are substantial, the approved imaging agents are being reimbursed as supplies. In addition, there is a continuing trend for imaging agents to demonstrate a positive impact on clinical outcomes. The clinical outcomes requirements combined with reduced levels of government reimbursement is increasingly challenging on new imaging agent development, even as gains in knowledge from genomics can now be translated into molecular imaging of critical disease pathways using radioactive molecules.

Imaging agents can identify the presence of disease but require a combination with appropriate treatment strategies to influence outcomes. Requiring imaging agents to impact patient outcomes before receiving reimbursement will make it increasingly challenging to develop imaging agents that will facilitate therapeutic agent development in less understood disease areas. Unfortunately these diseases are those that may benefit most from molecular imaging.

With respect to governmental reimbursement, the introduction of Ambulatory Payment Classifications (APC) packaging under the Outpatient Prospective Payment System (OPPS) continues to create challenges for imaging agent development. Some low cost, high usage imaging agents have been included with some low usage, high cost agents in the same APC. This has resulted in overpayment for low cost radiopharmaceuticals and significant underpayment for high cost agents. Many hospitals are reluctant to utilize imaging agents that result in a financial loss with each use due to packaging imaging agents with widely varying cost into the same APC. Without clarity that new imaging agents will be reimbursed at a level that reflects the cost, there may not be sufficient incentives for companies to introduce new imaging agents that advance patient care.

In addition to discovery, development, and governmental reimbursement, CORAR is concerned about supply of necessary medical isotopes currently only manufactured by reactors outside the United States. Following the Mo-99 shortage in 2009 and 2010, the member countries of the Organization for Economic Cooperation and Development (OECD) established a working group to address the future supply of Mo-99 (<http://www.oecd-nea.org/med-radio/>). In 2011, the OECD issued a policy statement with six principles for government and industry. The six principles

included the OECD recommendations on outage reserve capacity (to hedge against future Mo-99 shortages), HEU conversion to non-HEU sources, and full-cost recovery to ensure an economically sustainable Mo-99 supply chain. The OECD defines full cost recovery as the identification of all the costs of production and recovering those costs from the market.

Full-cost recovery will ensure that alternate manufacturers and suppliers of Mo-99 will be able to invest in the industry and enhance their ability to compete with government sponsored facilities operating at subsidized cost levels. CORAR believes that the concept of full-cost recovery establishes an important foundation to cover the significant costs that are being incurred by industry to implement new Mo-99 production capabilities while building adequate Mo-99 production capacity to protect against future shortages. In addition, the substantial costs associated with converting to non-HEU, in support of the Global Threat Reduction Initiative (GTRI) must be considered. CORAR believes that the development of new Mo-99 manufacturing capacity using non-HEU sources must be done in a way that allows industry to recover additional costs while attracting additional investment to support new production.

We recommend:

- 1) Initial FDA approval be based on demonstrating the imaging agent is capable of detecting the molecular target it was designed to measure
- 2) FDA approved imaging agents are automatically assigned a HCPCS level II code
- 3) The current pass through payment under OPSS should be designated to be for a full three year period in order to establish cost.
- 4) High cost and low cost radiopharmaceuticals should not be included in the same APC code through an appropriate application of the methodology used by CMS to ensure their payment groupings are appropriate with respect to clinical and resource considerations. This methodology is known as the “two-times” (2x) rule.
- 5) Continued collaboration between government agencies and industry stakeholders to support the reliable and sustainable supply of medical isotopes to meet the needs of US patients. This includes our request for accelerated rule making under the American Medical Isotopes Production Act of 2012 to promote a domestic supply of medical isotopes.

Thank you for your time and consideration to the issues above. If you have any questions or would like to discuss it further, please do not hesitate to contact [REDACTED]. We look forward to the continued dialogue with the Committee on the 21st Century Cures Initiative.

Respectfully,

[REDACTED]

Michael Guastella
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June 1, 2014

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

Via electronic submission: cures@mail.house.gov

Dear Chairman Upton and Congresswoman DeGette:

On behalf of GlaxoSmithKline (GSK), I am pleased to express our support for the Energy and Commerce Committee's 21st Century Cures initiative, and to submit our comments to the Committee's Call to Action white paper. GSK is a science-led global biopharmaceutical company dedicated to improving the quality of human life by enabling people to do more, feel better and live longer. An industry leader, GSK develops a broad range of innovative products in Pharmaceuticals, Vaccines and Consumer Healthcare. We applaud your efforts to create a mechanism for Congress to solicit proposals that would enhance the regulatory framework in support of biomedical innovation in the United States.

Innovative medicines contribute enormous health and social welfare benefits to individuals, as well as economic efficiency and competitiveness for society. A healthy population is also a more productive population. In this way, the biopharmaceutical industry positively affects a vibrant and productive workforce. The sector also provides substantial investment in research and development, leading to high quality jobs for science graduates, unrivalled job multiplier benefits, and support for the academic research community.

GSK employs approximately 17,000 employees in the U.S., we have two U.S. headquarters (Philadelphia, Pennsylvania and Research Triangle Park, North Carolina), six research and development sites (3 - Pennsylvania, 1 - North Carolina, and 1 - Massachusetts), and eight manufacturing sites (3 - pharmaceuticals and 5 - consumer healthcare). In 2013 GSK spent \$5.68 billion for research and development (40% U.S. based). Our major areas of research focus include respiratory, HIV, vaccines and consumer healthcare.

The information below details GSK's priorities in support of innovation, outlined within the framework of Discovery, Development and Delivery. We look forward to working in partnership with the Energy and Commerce Committee on this important initiative.

Discovery

A. Predictable and Sustained NIH Funding

The funding provided by the NIH to universities, clinical research institutes, government laboratories and small start-up biotech companies is essential for the understanding of the biological processes involved in the causation and treatment of disease, and for the development of tomorrow's researchers and clinicians. It is a matter of some concern therefore that there has been a significant slowdown in federal funding for research and that the resources available to NIH are now estimated to be at least 22% (\$4.7 billion) less in constant dollars than they were in 2003. Predictable and sustainable funding of high quality basic biomedical research and encouragement of effective industry/academic collaboration are key elements for the U.S. maintaining a leadership role in the discovery of innovative medicines for patients.

B. The importance of Public-Private Innovative Partnerships (PPPs)

No one category of stakeholder can solve the next generation of discovery challenges. These partnerships should be wide-ranging and include not only public-private partnerships but also cross-sectoral business partnerships. Critically, partnerships can be effective in tackling root causes of, and facilitating cross-sectoral solutions to, discovery challenges.

The changing nature of pharmaceutical R&D has led to companies such as GSK increasing the diversity of their research programs and increased collaboration with external groups – in academia and with other companies in the sector. It is essential that the industry is able to leverage NIH-funded science and technology in our search for new treatment and diagnostic modalities – and to support the translation of publicly-funded research into medicines of the future through innovative schemes and funding instruments supported by NIH that encourage all parts of the innovation eco-system to work more closely together, such as the recently announced Accelerated Medicines Partnership (AMP).

The AMP, in which GSK will be participating in the Alzheimer's section, is a good example of a PPP that will help deliver the objectives of the 21st Century Cures initiative. Diseases such as Alzheimer's are too complex to be solved by any one organization. The AMP will address this challenge by bringing together the scientific know-how from biopharmaceutical, academia and non-profits partners to enable a rapid acceleration in the identification and validation of new biological targets of disease.

We welcome the desire of the 21st Century Cures initiative for the U.S. to maintain a leadership role in the translation of basic biomedical research into potential therapies through such PPP programs, but we would strongly suggest that the Committee be aware of other government sponsored PPPs, helping to limit duplication of effort at a time of global budgetary challenges. In this context, GSK is pleased to note that NIH AMP has been active in looking for areas of collaboration with other key PPPs such as the Innovative Medicines Initiative (IMI), co-funded by the European biopharmaceutical industry and the European Union.

One example of effective industry-academia collaboration is our collaboration with Yale University, which aims to design a potential new class of medicine that degrades disease-causing proteins. The collaboration combines GSK's expertise in medicinal chemistry with Yale's pioneering work on proteolysis targeting chimeric molecules (PROTACs). This partnership is exploring a new way for promising, but unproven therapeutic approaches to jump from the academic lab more quickly into the early stage pharmaceutical pipeline.

Another such example is with our recent focus into the area of Bioelectronic medicine - where nano-scale devices connect to groups of individual nerve fibers and change patterns of electrical signals to restore health to organs and biological functions.

In 2013, the GSK Bioelectronics R&D unit agreed with 15 academic groups across the world to enter exploratory research projects. We are continuing to expand the Exploratory Funding Program to new groups during the first half of 2014 with funding decisions occurring on a rolling basis after a one-month review and approval process. The goals of this program are outlined below:

1. Help principal investigators (PIs) around the world swiftly initiate research in areas that could underpin future bioelectronic medicines
2. Allow GSK and a network of PIs to get to know each other through actual work over the course of a year
3. Help GSK Bioelectronics R&D explore the potential of this emerging area

We believe that bioelectronic medicine will open up a whole new front in our mission to control and reverse disease. Our goal is to have the first medicine that speaks the electrical language of our body ready for approval by the end of this decade.

We would also like to bring to the attention of the Committee our long standing collaboration with the Harvard Stem Cell Institute (HSCI). This unique alliance, initiated in 2008, has shaped our discovery scientific priorities in regenerative medicine including projects aimed at neurogenesis, motor neuron diseases (ALS), ophthalmology, muscle rejuvenation and hematopoietic stem cell (HSC) transplantation. The collaboration between GSK and HSCI scientists has delivered new advances in human induced pluripotent stem cells (hiPSC) and will potentially lead to novel drug discovery approaches.

To ensure that these industry-academia collaborations are able to bring innovative medicines to patients in the U.S., we would highlight to the Committee that access to and interaction with leading academics as advisors is vital, and should not be viewed as a conflict of interest. It is important, for both sides, that these interactions are encouraged under appropriate processes.

C. U.S. Leadership - Medical Challenges

The Office of Science and Technology characterizes grand challenges as ones that are ambitious but achievable goals that harness science, technology, and innovation to solve important national or global problems and that have the potential to capture the public's imagination. We believe the issue of antimicrobial resistance and the dearth of innovative products in this area meets the grand challenge criteria. The President's Council of Advisors on Science and Technology (PCAST) is due to issue a report on antimicrobial resistance and ecosystem issues, which highlights key concerns and challenges within the antibiotic drug development process, including drug discovery, development, approval and marketing.

The growing threat of antibacterial resistance and the complexities of this area increasingly demand a collaborative response, moving beyond the scientific community to include policy makers, healthcare payers, academia, regulators and healthcare professionals.

Antibiotic resistance and the lack of new antibiotics in development are serious threats to our nation's public health, patient safety, and national security. The U.S. needs high level leadership and a comprehensive action plan, including well-defined goals and timelines for activities, to address antibiotic resistance and the stagnant antibiotic pipeline. Efforts to address resistance must involve all relevant government and non-government stakeholders. There is an urgent need for new antibacterial agents. The spread of resistance to antibacterials has become a global threat to public health, reducing the options available to healthcare providers to manage life-threatening infections. As well as managing traditional sources of infection, many modern medical interventions such as chemotherapy, acute cardiac interventions, elective surgery, transplantation and care of neonates require effective antibacterials. The lack of accurate rapid diagnostic tests that can be used to identify pathogens before antibiotics are used makes the problem worse, as doctors have to prescribe based on symptoms, rather than confirmed bacterial infection.

The current marketplace fails to incentivize investment in antibacterial research and development (R&D) sufficiently. In 1990, there were almost 20 pharmaceutical companies with large antibiotic R&D programs. Today, there are only five large companies and a handful of small companies remaining. Three key challenges have caused a number of biopharmaceutical companies to discontinue R&D investment in this area and have contributed to a lack of new antibacterials in development:

1. Unique scientific challenges associated with antibacterial discovery research
2. Evolving, uncertain regulatory requirements
3. A relatively low prospect of a reasonable return on investment

Our strategy at GSK is to pursue antibacterial R&D research via collaborations and funding partnerships working with other companies, academia, and funding bodies such as the Innovative Medicines Initiative (EU), The Wellcome Trust, the Biomedical Advanced Research & Development Authority (BARDA – U.S. Government) and the Defense Threat Reduction Agency (U.S. Government). In the U.S., BARDA has helped revive a dormant antimicrobial drug industry to develop novel antibiotics with eight candidates in the BARDA pipeline and combat growing antimicrobial drug resistance.

To continue this initial progress and ensure companies do not redirect their research efforts to other areas, a strong federal funding commitment is needed.

Development

Moving potential new medicines from the discovery phase into development requires large financial and time commitments from biopharmaceuticals companies. In order to be successful in delivering new cures and medicines to patients, this commitment must leverage the innovative advances in development sciences and have policies in place to ensure that these new advances are appropriately supported. Below we outline some key development areas that could help bring innovative cures into the 21st century.

A. Modernization of Clinical Trial Designs

Advances in clinical design methodology and regulatory thinking present opportunities to increase the quality of our clinical programs, optimize decision-making and reshape the economics of development. GSK aims to strengthen and deliver the design and implementation of patient-centered, efficient clinical trials by the systematic use of novel design approaches and tools such as model-based development, futility, and predictive inference, use of historic data, Bayesian analyses and adaptive and enriched population designs. This will offer opportunities to deliver effective medicines to patients while improving ROI, enabling us to focus resources in areas where patients may benefit the most.

It is important that industry and regulators work together to advance clinical trials designs methodology. A specific example is adaptive design, which allows medicines to be evaluated and progressed with greater confidence or alternatively allow for early termination of ineffective medicines, thereby decreasing patient exposure to medicines which have no benefit for them.

In this context, GSK would support increased FDA acceptance of data from novel (other than randomized/controlled) adaptive trial designs employing Bayesian statistical methodology, as well as, improved FDA acceptance of adaptive trial designs for phase III clinical protocols and increase acceptance rates of protocols reviewed under the FDA Special Protocol Assessment (SPA) process.

B. Adaptive Pathways

New approaches that help accelerate access to new medicines for patients with serious medical needs are welcome. The FDA Breakthrough Designation and increased scope of the Accelerated Approval pathway are promising developments for patients with the highest need. However the concept of Adaptive Pathways, which is under discussion globally and being piloted in Europe, has a goal of accelerated and predictable access to all appropriate patients, through iterative and adaptive cycles of development and review. Engagement from not only FDA, but also CMS and private payers, and healthcare professionals and patients during design and implementation of the development strategy is critical. Following an earlier approval for a high need population, subsequent access to a broader population could, in theory, be supported by data not just from RCTs, but derived from combining evidence from close monitoring of the real-world use of the product and trials of pragmatic design (once the product has an initial indication, more efficient options become available for generating this data). By negotiating the requirements for clinical data with all stakeholders, iteratively, the total evidence programme can be significantly streamlined.

GSK has played an important role in progressing this topic at MIT's NEWDIGS multi-stakeholder forum and believes this approach offers considerable potential. We recognise several concerns that need to be addressed via continued engagement with stakeholders at NEWDIGs, the EMA pilots and elsewhere. Firstly the role, analytical techniques and limitations of real world data need to be better defined and agreed by all. We are pleased with the work undertaken by organizations like ONC, PCORI, OMOP, mini-Sentinel and other initiatives into these issues, but GSK would welcome increased FDA engagement on this important topic. Secondly, a careful balance is needed to manage the use of a product after the initial approval (which is often in a limited patient population). FDA is rightly concerned about possible off-label use whereas physicians need to be equipped to make decisions in the best interests of individual patients. Patients are increasingly vocal on the need for

access to new medicines earlier and their willingness to accept greater uncertainty in doing so. We believe such access delivered by an initial approval under an adaptive pathway is preferable to expanded compassionate use programmes or other pre-approval schemes.

The development of novel antibacterials is one area that will benefit greatly from adaptive regulatory pathways. The EMA has recently taken specific steps to address the challenges faced in developing antibacterials (including publishing guidance to facilitate studies and clinical development programmes, consulting on revision of its guidance on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products, and the adaptive licensing pilot discussed above). We would encourage the Committee to do the same through supporting the passage of H.R. 3742, the *Antibiotic Development to Advance Patient Treatment (ADAPT) Act*, which intends to allow for a greater use of alternative trial endpoints, and stronger reliance on preclinical and clinical data in combination with human efficacy studies, which should bolster the capacity and speed with which new antimicrobials are developed.

C. Clinical Trial Data Transparency

There are important scientific and patient benefits that can come from greater sharing of data that have been collected in clinical research. These data can be used in further research to validate findings, generate hypotheses, and gain greater insight into the progression of disease and the risks and benefits of medicines. To help realise a goal in which data collected by the biopharmaceutical industry and academic centers are shared, GSK led the way in launching a system in May 2013 where researchers can request access to patient level data from GSK's clinical trials, extending back to 2000. After a proposal is accepted by an independent external review panel, researchers are provided access to the data and analytical software. To facilitate researchers' access to clinical trial data and the ability to combine data across different sponsors, GSK have expanded the clinical trial access system to include studies conducted by seven industry study sponsors (<https://clinicalstudydatarequest.com/>). It is our hope that other biopharmaceutical and academic sponsors will join. We welcome the Committee's efforts to encourage other study sponsors and in particular those in academia to share patient level data for further research, as well.

D. Precision Medicine and Diagnostics

Precision medicine is the acquisition and use of molecular data from patients and the association of these data with response to therapy. This is being made possible by the falling cost of next generation sequencing, by adopting emerging technologies and process changes, and by accessing the "big data revolution" in healthcare. By leveraging biomarker discovery and testing, and translational research, the biopharmaceutical industry will be able to deliver better patient selection, better benefit-risk and better patient outcomes; a better value proposition for multiple stakeholders, including payers; and more cost-effective drug development.

The development of precision medicines requires access for researchers to biological samples, linked to genomic and clinical data from which personally identifiable information has been removed. The development of bio banks, linked to comprehensive electronic patient records, would help to advance the discovery and development of precision medicines. It will also be important to ensure that patients and physicians understand the potential benefits of precision medicines and have access to testing to determine whether patients are eligible for precision medicines.

We see positive developments in regulatory policy, however in order to fully deliver the promise of precision medicine, changes in the post-regulatory environment will be required, such as modernization of reimbursement codes to align with greater and more sophisticated diagnostic and companion diagnostic testing, health information technology to facilitate evidence generation on clinical outcomes, and incorporation of personalized medicine and diagnostic concepts into medical education curricula.

Furthermore, it will be increasingly important for the Agency to continue to advance the regulatory framework to support adoption of multi-analyte patient screening and companion diagnostics (e.g. Next Generation Sequencing) that leverages, not only the advances in technology, but also the application of a wealth of data to aid identifying the right patient(s) for the right treatment(s). GSK would support the specific recommendations below:

1. Streamline and accelerate FDA processes for qualifying biomarkers for defining patient populations most likely to derive benefits from targeted medicines.
2. Clarify FDA's evidentiary standards for qualification of biomarkers and companion diagnostics and accelerate the timelines associated with the qualification process.
3. Improve the coordination and communication across FDA Centers working in parallel to review/approve targeted medicines and their companion diagnostics (CDER, CBER, CDRH).
4. FDA approval of Next Generation Sequencing as a validated way to detect gene changes as biomarkers, rather than to approve every single individual test.

E. Food and Drug Administration

Development of innovative medicines for patients is dependent on a healthy and well funded FDA that has the capability to keep pace with the latest scientific advances. GSK commends the FDA's commitment to maintaining its high standards, even during fiscally challenging times. We have worked closely with the FDA this past year, achieving 6 new approvals of important medicines for patients. Although we believe the FDA is well positioned to support the innovation needed for 21st century cures, there are some areas that can be improved upon to benefit patient's access to medicines. Below are specific recommendations:

1. PDUFA

The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 and has been subsequently renewed in multiple five year terms. PDUFA authorizes the Food and Drug Administration (FDA) to collect user fees from the pharmaceutical industry that supplement, but do not replace, Congressional appropriations. The fees are used by the FDA to ensure a timely, scientifically robust drug approval and review process. GSK supports the role PDUFA plays in bringing innovative new treatments to patients without unnecessary delay and strongly supports legislative efforts to permanently exempt user fees from being sequestered.

2. Patient Reported Outcomes (PROs)

GSK has a strong focus on the patient and supports efforts to work with regulators to validate clinically meaningful PROs and to capture the patient's perspective through Patient Focused Drug Development (PFDD) interactions. We believe further progress is possible, and would specifically support:

- Developing more efficient/timely FDA processes for qualifying PRO measures.
- Establishing clear evidentiary standards for qualifying PROs for inclusion in Phase III clinical protocols.
- Improving the levels of coordination and communications between FDA Review Divisions and the Study Endpoints and Labeling Development (SEALD) group.
- Building a clearer/stronger linkage of PRO process to FDA Patient Focused Drug Development initiative currently ongoing under PDUFA V.
- Recommending the FDA begin to consider how they will handle unstructured real time data coming from patients during the course of clinical trials (i.e. "patient listening" in trials).

3. Regulatory Expertise and Continuous Improvement Culture

GSK supports regulatory agency efforts to enhance expertise in new/emerging areas of science, medicine, information technology, epidemiology and statistics. We also support the need to develop a "continuous improvement culture" to expedite the transfer of benefits derived from novel/expedited pathways to a broader set of product development programs.

Delivery

A. Reimbursement for Innovation

Healthcare innovation transforms the lives of individuals. The mother with cancer given more time with her children by new treatments; the child living a normal life thanks to inhaled steroids for asthma; children protected by vaccines from once killer diseases; grandparents leading healthier lives; the African child who has hope of protection from malaria, thanks to a new vaccine.

Innovation can drive growth and competitive advantage - through high quality jobs, support for academic infrastructure in our universities, and healthier, more productive citizens. We need policies, interventions and collaborations which allow the biopharmaceutical sector to transform and deliver to the needs of the 21st century.

We recognize that those who purchase our medicines want value for money. It is appropriate that evaluation mechanisms are in place to assess the impact/added value of healthcare interventions, including medicines, on patients, society and the total healthcare system. These evaluations should not, however, act purely as cost-containment or delay mechanism.

GSK supports the assessment of value to encompass a range of criteria reflecting important constructs including - clinical benefits, patient benefits and societal and public health benefits.

B. Strengthening Legislation and Economic Incentives

Driving innovation through federal legislation and economic incentives can play a vital role in solving the most pressing challenges facing our society. For example, earlier this year, H.R. 4187, the *Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms* (DISARM) Act was introduced. This legislation intends to improve the reimbursement environment for new antibiotics that treat the most significant infection threats. The *Generating Antibiotic Incentives Now* (GAIN) Act from 2012 provided economic incentives (five years of additional data exclusivity for a total of 10 years) and a faster path to market (approval on Phase 2 data) for developers of antibiotics for hard to treat infections. The DISARM Act will further this much needed development.

New approaches to rewarding antibacterial R&D investment and reimbursement are required to maintain investment from biopharmaceutical companies still active in antibacterial R&D, and to attract new entrants:

1. In the short-term, the curative and life-saving value of existing and emerging antibacterials needs to be adequately reflected in pricing policies.
2. In the longer-term, an economic model that encourages antibacterial R&D investment by overcoming the recognized market failures is needed. De-linking the reliance on sales volume as the key driver of economic returns could help achieve this.

Payment incentives, coupled with incentives for drug development can be a powerful combination in promoting innovation.

C. Harnessing the Digital Era for Patient Benefit

Driven by technological advances in mobile communications, data analytics, biosensors and more, the field of digital healthcare is taking shape now and advancing rapidly. A combined and coordinated application of these new technologies could ultimately control the increasing burden of healthcare, speed up development of new therapeutic drugs and increase the quality and value of the patient-centered healthcare data allowing for a deeper understanding of patients' disease and well being. A future state where established U.S. organizations (HCPs, pharmaceutical companies, hospitals, diagnostic companies) collaborate and synergize with current generation technology companies (electronics, internet providers, e-commerce, genetics companies, IT providers) to develop a holistic and predictive approach to healthcare, using in depth patient insights, combined with powerful analytics could revolutionize how diseases are prevented and managed. For example:

1. Continuous remote measurement of patients to better understand disease and response to treatment in real time/real world setting
2. Use of multiple digital channels and platforms for deeper and broader engagement: both with patients, as well as with HCPs

This new way of operating as an overall healthcare ecosystem could then provide new targets for novel therapies and continually fuel the creating of targeted medicines to prevent and treat disease. In support of the new operating digital ecosystem, GSK supports providers' use of HIT tools, including electronic health records (EHRs), to encourage high-quality care delivery through accurate and transparent documentation and the use of evidence-based guidelines to establish care protocols. GSK recognizes that health

information technology (HIT) will play an essential role in changing the current state of the U.S. health care industry.

GSK supports federal legislation and regulations that encourage bold incremental adoption of HIT (e.g. Electronic Medical Records, Health Information Exchange) which ensures achievable and sustainable system advancement. We recognize and champion HIT initiatives that support delivery and payment reform in tandem with technology ventures with the understanding that improvements in quality and efficiency are mutually dependent on parallel adoption.

GSK continues to support secure, interoperable, and standardized health information exchanges that enable better care coordination, quality measurements, public health improvements, and clinical research while facilitating public-private collaboration. Furthermore, we believe that engagement of and access to clinical population data should be transparent and a shared community asset that encourages a competitive value-based marketplace that incentivizes innovation.

Health Information Technology has been recognized as a key building block for the infrastructure of delivery system transformation and one of the most promising tools for improving overall quality, safety and efficiency of the health delivery system.

D. Coordinated Care for Chronic Disease Management

Given the role chronic disease plays in impacting patient outcomes and overall U.S. healthcare costs, a systematic approach to medication management is needed to close the gaps in care and optimize patient outcomes. However, our current delivery and payment models have failed to integrate a comprehensive medication management service that achieves these goals.

Comprehensive Medication Management (CMM) is an innovative and collaborative solution to this issue: CMM is a patient-centered, coordinated approach to drug therapy that has been shown to help optimize clinical and patient goals of therapy in a safe and effective manner, improving clinical outcomes and quality while reducing overall healthcare costs.

CMM is the standard of care that ensures each patient's medications (prescription, nonprescription, alternative, traditional, vitamins, and nutritional supplements) are individually assessed to determine the medication is appropriate, effective for the medical condition, safe given the comorbidities and other medications being taken, and the patient is able and willing to take the medicine as intended.

GSK supports the adoption of Federal regulation and implementation of CMM and believes it should be integrated into new and existing models of coordinated care.

E. Value of Vaccines

No other health intervention is as simple, powerful and cost effective as a vaccine. Over the past thirty years advances in science, business and distribution have transformed the field to the point where vaccines are recognized as a "best buy" in global health, a driver of biopharmaceutical industry growth and a key instrument in international development.

Vaccines have protected billions of people from the scourge of previously deadly and debilitating diseases that threatened populations across the globe. For example, smallpox

was eradicated in 1979; polio cases fell by over 99%, from over 300,000 per year in the 1980s to fewer than 2,000 in 2009; and the number of reported measles deaths has dropped from 6 million to less than 1 million per year. Experts have suggested that vaccines have saved in the vicinity of 20 million lives in the last two decades.

Despite the need and ability to protect adults from preventable infectious diseases, vaccination rates among adults remain low. The good infrastructure for vaccinating children and awareness of the benefits of childhood vaccinations have boosted vaccination rates among children and lowered death rates from vaccine-preventable diseases. Achieving higher vaccination rates among adults offers a significant opportunity to reduce the human and financial costs of diseases that could be prevented by vaccines.

Improved access to and uptake of adult vaccines has the potential for significant economic and social returns for public health overall. GSK supports public policies that improve access to and awareness of recommended immunizations for adults. Its success requires a rethinking by all stakeholders of traditional approaches to immunization programs and budgets. This re-evaluation needs to be built on an appreciation of the value of prevention to economies and to recognize the substantial research and development costs associated with the new wave of vaccines.

F. Evidence Communication

Stakeholders continue to push toward better ways to achieve high-value healthcare, increasingly calling for new approaches to support value-based decision making and promoting public health. Evidence is an essential component of value-based healthcare, helping payers and other stakeholders make informed choices about which medical interventions and clinical uses of drugs will best meet individual and collective patient needs. In recent years, the drive to enhance value in healthcare has manifested in an increased interest on the real-world relative risks and benefits of clinical options, including studies in comparative effectiveness research (CER).

For the biopharmaceutical industry, these developments create new imperatives to ensure that research investments adequately capture new definitions of value and anticipate how evolving use of real-world evidence affects the decisions of population health decision makers, ultimately affecting patient care and health outcomes. Informed treatment decisions necessitate full, timely access to accurate, balanced information that reflects the rapid expansion of types and sources of evidence.

Increasingly, healthcare decision makers including payers, providers, and patients are asking questions about how healthcare products and services work in "real-world" settings, as opposed to controlled clinical settings. Specifically, decision makers are increasingly interested in understanding how products may impact patient outcomes including quality of life, whether they are cost-effective, and if any longer-term safety issues are seen during "real-world use" as opposed to the ideal but limited settings that are evaluated in randomized clinical trials (RCTs).

The generation and collection of real world evidence (RWE) supports the company's discovery and development of medicines that fulfill important clinical needs, as well as ensuring our medicines are used appropriately to benefit patients and maximize health outcomes. GSK believes that RWE is an innovative way to help improve patient care by filling gaps in evidence about the use of healthcare products and services in real-world

settings that randomized controlled trials used to support product approvals may not address.

During this period of fundamental shifts in the U.S. healthcare system, health insurers and other population based decision makers require full information regarding medical care and research available in real time. Currently biopharmaceutical manufacturers are limited to only proactively communicate evidence directly on a product's label as a legal and regulatory matter. This inability of industry to freely engage in communication of research findings at par with other US researchers and institutions undermines the foundation of the US public health. GSK believes that RWE (including CER) can help provide more complete information for better patient care by filling gaps in evidence about the use of healthcare products and services in real-world settings and therefore strongly support FDA regulations for proactive communication of RWE by biopharmaceutical companies.

Additional Considerations

A. Ensuring a Balanced Approach to Intellectual Property Rights

GSK respectfully requests the Committee recognize the key role that intellectual property (IP) plays in supporting and driving innovation; in helping the biopharmaceutical sector to meet unmet medical needs; and in providing a framework for small and medium sized enterprises to flourish. A balanced IP system is necessary to provide incentives for the high risk and high cost of developing new medicines and vaccines. It creates the conditions under which industry can generate the returns needed to fund R&D, including for diseases that disproportionately affect the developing world. IP rights drive innovation and investment and ensure a level playing field between developed and developing countries, to the benefit of patients and economies around the world.

The research-based life science industry is virtually unique in being required to provide significant amounts of confidential test data (such as preclinical and clinical data) to regulatory authorities as part of the product registration process. Data Exclusivity recognizes the proprietary nature of this data by ensuring that it is not referred to by other companies (for a defined period) when they are registering their products and, even after that defined period, it remains confidential. This protection provides incentives for the substantial financial investment involved in generating the data in the first instance.

GSK believes the Committee should consider revisions to the current patent laws in the U.S. to be more competitive with the global research and development environment.

Investment in the discovery of new medicines is a costly and long term effort and innovators need business certainty that such investment will yield a predictable return. A reasonable period of time to recoup the investment is critical to research funding and a sustainable business model. The current period of Data Exclusivity is inadequate to support the de novo development of new medicines and new technologies, especially in areas of high-risk research. Harmonizing the data exclusivity periods applicable to drugs approved under section 505(b) of the FDCA and biologicals approved under section 351 of the Public Health Service Act would encourage investment in new therapies. The U.S. has fallen behind Europe, which grants up to 11 years of data exclusivity for new drugs, in providing such incentives, and the Committee should consider the extending the period of data exclusivity for 505(b) drugs.

In addition, the Committee should consider targeted data exclusivity incentives to encourage development of medicines to meet significant unmet medical needs. An example is the extended data exclusivity provisions proposed in H.R. 3116, the *MODDERN Cures Act of 2013*, which can stand apart from any patent provisions. Incentives to develop companion diagnostics, another feature of the *MODDERN Cures Act*, will stimulate research aimed toward ensuring the right medicines reach the right patients. A consequence of such research will be cost efficiencies in the delivery of healthcare, since only the most responsive patients will receive the new medicines.

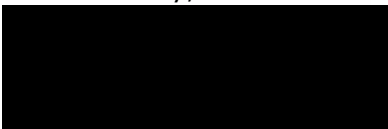
Additional incentives to innovate may be provided via enhanced patent protection or via tax relief or credits for R&D expenditures. An example of a tax incentive is the "patent box" that has been implemented in the U.K. and introduced in H.R. 2605, the *Manufacturing Innovation in America Act of 2013*. Such measures would make the U.S. a more desirable place to do research and would effectively reward investment in R&D generally. Measures to enhance patent protection for medicines have been discussed frequently and could include day-for-day restoration of patent term to compensate for regulatory delay, lifting of the 5 year limit on patent term restoration, and lifting of the 14 year from approval cap on total patent term if restoration is applied

Conclusion

GSK's mission is to enable people to Do More, Feel Better and Live Longer. We have an important role and responsibility in improving the health of people around the world. Innovative medicines and vaccines contribute enormous reassurance for individual citizens, and increased economic efficiency and competitiveness for society. The most important thing GSK can do is discover, develop and deliver products that address unmet need and improve quality of life – and to work with others to make these medicines accessible as soon as possible to people who benefit from them.

We commend the Committee for examining ways to deliver greater alignment between the biopharmaceutical industry and regulators to ensure the U.S. continues as the world leader in delivering innovative products to patients. The discovery, development, and delivery cycle is crucial to this process. We sincerely appreciate the opportunity to comment on the 21st Century Cures initiative and look forward to continued discussion and input with the Committee.

Sincerely,



Moncef Slaoui, PhD
Chairman, Global Research & Development and Vaccines

**Global Health Technologies Coalition Feedback on the 21st Century Cures Initiative Call to
Action white paper**

Energy and Commerce Committee

US House of Representatives

May 30, 2014

Kaitlin Christenson, Coalition Director, Global Health Technologies Coalition

21st Century Cures: A Call to Action

Dear Chairman Upton, Congresswoman DeGette, and members of the Committee, thank you for the opportunity to provide comments on the Energy and Commerce Committee's white paper, *21st Century Cures: A Call to Action*. I am submitting these comments on behalf of the Global Health Technologies Coalition (GHTC), a group of nearly 30 nonprofit organizations working together to advance US policies that can accelerate the development of new global health innovations—including new vaccines, drugs, diagnostics, microbicides, multipurpose prevention technologies and other tools—to combat global diseases and improve health. Our comments reflect the research and experience of our member organizations, which include nonprofit advocacy organizations, policy think tanks, implementing organizations, product development partnerships (PDPs), and many others.

Health at Home in an Interconnected World

The Centers for Disease Control (CDC), the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) all play critical roles in the development of new products used to improve health in the developing world. We appreciate the Committee's resolve to finding new ways to accelerate the pace of new cures and medical breakthroughs here at home, and believe that in today's world, the health of Americans is interdependent with the health of populations abroad. Health threats know no borders, and protecting the wellbeing of Americans now requires a global effort. Global diseases are often a plane ride away, or in some instances, still a threat in the United States. For example, both dengue fever and Chagas disease have made resurgences in some states, and malaria and drug-resistant tuberculosis (TB) cases are on the rise. While advancements have been made, new technologies for the effective diagnosis, treatment, and prevention of these diseases are greatly needed. For instance, newer, more robust, and easier-to-use antiretroviral drugs—particularly for infants and young children—are needed to treat and prevent HIV, and even an AIDS vaccine that is 50 percent effective has the potential to prevent one million HIV infections every year. Drug-resistant TB is on the rise in the United States, but the only vaccine on the market has not halted the global epidemic and because of its lack of efficacy, the United States does not recommend it for use. In addition, most TB drug therapies available today are more than 50 years old and extremely toxic. Additional new information indicates that several neglected tropical diseases (NTDs) are now affecting large numbers of people living in poverty on the Gulf Coast—including dengue, West Nile virus infection, Chagas disease, cysticercosis, and toxocariasis, with the expectation that Chikungunya virus infection will also emerge soon. Cities along the Texas Gulf Coast appear to be particularly vulnerable and Houston has now emerged as the first major US city with endemic dengue fever. These diseases are now among the most important health disparities in the southern US. US health research in these areas has a direct impact in ensuring Americans have access to modern and effective drugs

and treatments. Below you will find input and feedback on many of the themes and questions raised in the Committee's May 1st white paper, *21st Century Cures: A Call to Action*.

The Role of Public-Private Partnerships in Development and Delivery

Public-private partnerships play a key role in accelerating and often filling a much needed gap to incentivize investment in products. One of the most successful and innovative collaborative models we see in the global health field has been through PDPs. PDPs are a unique form of public-private partnership established to drive greater development of products for neglected diseases and conditions. PDPs leverage both private and public funds and expertise and fill a critical gap where markets are not lucrative and industry cannot expect sufficient returns to justify capital-intensive research and development (R&D) investment. From 2000 to 2010, PDPs accounted for more than 40 percent of new global health products registered. One example of this model and its global impact is through the development of a new, accurate, and easier-to-use TB diagnostic, Xpert MTB/RIF. In 2008, 1.6 million TB cases went unreported, in part because of the difficulty of diagnosing this disease. In 2006, a PDP called Foundation for Innovative New Diagnostics (FIND) partnered with Cepheid, a private company in California, and the University of Medicine and Dentistry of New Jersey to develop and test a new diagnostic test for drug susceptible and drug-resistant TB. The result was Xpert MTB/RIF, a cartridge used on the fully automated molecular diagnostic platform GeneXpert. There is no need for microscopes or a laboratory, it is simple to use, 98 percent accurate, detects drug-resistance, and can diagnose TB in HIV-infected patients (people with HIV are 20 to 30 times more likely to develop TB). The result: patients can now start appropriate treatment on the same day, rather than waiting weeks for laboratory results or undergoing a year of failed therapy if they have undiagnosed MDR-TB. Xpert MTB/RIF was developed by FIND, Cepheid, the University of Medicine and Dentistry of New Jersey, with funding from the Department of Defense (DoD), NIH, and the Bill & Melinda Gates Foundation. The US Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief have supported its roll out in developing countries.

As of 2013, PDPs have been involved in the development, evaluation, or introduction of 42 global health technologies. More can be expected from PDPs in the future with sustained and additional support. Currently PDPs report being involved in the development of more than 450 technologies aimed at addressing a variety of global health needs in various stages of development.

Consistency and Coordination to Accelerate Innovation

The US government is currently involved in 200 of the 365 global health products currently in the pipeline. Multiple agencies, which include the NIH, CDC, FDA, DoD, and USAID are all involved in the process. While various agencies are involved at different points of the process, two-thirds of US government funding is directed at early stages of the R&D spectrum and only one-fifth goes to clinical studies in humans. While early stage funding is critical, without adequate late-stage funding, these products never make it to market. Final clinical stages of product development are the most expensive and are the most in need of funding. Because global health products are being developed for use in the developing world and don't offer lucrative commercial markets, government support for later stage trials is imperative and helps ensure

accountability across the spectrum. US funding for global health R&D is not only critical to those in the developing world—sixty-four cents of every US dollar invested in global health R&D benefits US-based researchers, many of whom conduct their research at American universities. In addition to investment across the value chain, US government efforts can be leveraged with improved coordination and recommend the creation of a cross-US government global health R&D strategy to help ensure that US investments in global health research are efficient, coordinated, and streamlined.

Leveraging the Role of NCATS in Development and Delivery

The National Center for Advancing Translational Sciences (NCATS) has great potential to accelerate the development and delivery of life saving tools and to play a much needed role in global health research. However, we remain concerned about the legislative mandate limiting NCATS in their clinical trial work. The Center is currently limited to supporting clinical trial activities only through the end of Phase IIA, with a special exception given to support some trials through the end of Phase IIB. NCATS is the only NIH center to be limited by a legislative mandate in its clinical trial work. There must be a balance between public- and private-sector funding for research, however there is no risk of NCATS duplicating the global health activities of private industry as this sector does not typically target neglected diseases due to small commercial markets. Neglected disease research was one of NCATS' stated areas of focus and we fear the current mandate is an unnecessary barrier towards reaching NCATS mission of delivering treatments to patients faster.

Strengthening the FDA's Impact and Removing Current Barriers

The FDA can play a particularly unique role in ensuring the conduct of high-quality research, monitoring clinical trials, registering new products, and expediting the introduction of global health tools. Some of the significant challenges PDPs face in the development of new products includes the management of complex multi-country clinical trials, which must be conducted in the regions where diseases are endemic, and the range of regulatory barriers that come with that challenge, including onerous application processes and lengthy reviews. In addition to the challenges faced abroad, global health product development can involve unprecedented regulatory hurdles in the US. In these situations, early and frequent communication between regulators and product developers is essential to the quality and efficiency of the regulatory system. Additionally, capacity to conduct as well as adequately regulate clinical trials does not exist or is often weak in most countries where neglected diseases are endemic. Finally, the approval process for new products for neglected diseases is poorly coordinated and involves multiple, complex steps. Global regulatory systems are not sufficiently streamlined and the capacity of regulatory authorities to approve products for the developing world is frequently weak. Therefore, regulatory review and introduction of new, safe, and effective products may take longer than necessary and increase the costs of research.

In an effort to help address regulatory issues worldwide, the FDA has played an increasingly critical role in global health over the past several years. For example, the FDA recently issued Breakthrough Therapy Designation to a new malaria drug, Tafenoquine, which may prevent infections from the *p. vivax* malaria strain, which will accelerate the regulatory review of the

drug. Additional support has primarily taken the form of leading numerous international programs, as well as building global regulatory partnerships to better coordinate regulatory activities worldwide and equip local regulatory authorities with the skills they need to independently facilitate medical product reviews. And as a stringent regulatory authority, the FDA's review of products can often facilitate subsequent review in the countries where the products ultimately will be used.

Despite these successes, there are still several areas where the FDA can build upon its recent activities to make the biggest possible impact on the lives of people around the world. For instance, several NTDs—one example being Chagas disease—are currently not on the list of global health conditions for which the FDA is legally allowed to conduct accelerated reviews of health products. The agency should therefore ensure its authority to review health products for all neglected diseases. Similarly, the creation of an office of neglected diseases in the Office of the Commissioner would help ensure that neglected diseases and global health issues are consistently elevated at the leadership level. Other changes, like the establishment of an informal mechanism to better communicate with product developers of global health technologies would assist in overcoming the unique barriers that these organizations face in seeking regulatory approval.

Conclusion

We share the Committee's passion for accelerating and improving the current process of discovery, development, and delivery. We stand ready to work with you on these important issues that are essential to saving lives and ensuring US leadership in today's global society. On behalf of the members of the GHTC, I would like to extend my gratitude to the Committee for this opportunity to provide feedback. Please do not hesitate to contact us should you have any questions.

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IN MEMORIAM
ROBERT T. ANGAROLA
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May 30, 2014

BY E-MAIL

The Honorable Fred Upton
Chairman
Energy & Commerce Committee
U.S. House of Representatives
Washington, DC 20515

The Honorable Diana DeGette
Energy & Commerce Committee
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Upton and Representative DeGette:

We are writing to you regarding how the Food and Drug Administration (FDA) can accelerate the approval or clearance of innovative devices. There are many different aspects to this topic. We wish to focus on two interrelated elements: product jurisdiction and the lack of clear guidance as to when a product is a device.

A fundamental element of the Federal Food, Drug, and Cosmetic Act (FDC Act) is that product regulation is a function of product classification. For example, devices are regulated differently than drugs or biologics. Congress has carefully defined these product classifications, and then established the regulatory requirements that apply to each specific classification. The regulatory requirements applicable to devices differ materially from those of drugs.

It is critical for companies to know as early as possible whether their products will be regulated as devices or not. Product classification directly influences many key decisions at an early stage, such as product development, budget, and timelines. Companies need to have certainty as to how their products will be regulated.

Recently, a number of companies with innovative products that they believed were devices have encountered significant problems with FDA's approach to classifying products. More specifically, based on established precedents set by FDA in regulating other products, these companies anticipated that their products would be regulated as devices, and proceeded accordingly with their development and commercialization plans. In some instances, companies had developed products that functioned in the same manner as products regulated by FDA as devices, and then were told their products would be regulated as drugs or biologics. In other instances, the product had already been regulated as a device and then FDA stated that future uses would be regulated as drugs or biologics.

These changes in regulatory approach all share a common feature: an abrupt change that is not incorporated or explained in established, publicly articulated policy. Rather, FDA has been making these product jurisdictional changes in an ad hoc manner based on unarticulated criteria. When pressed to explain its reasoning in individual cases, FDA has advanced theories that do not track the statutory language, existing regulations, existing guidance documents, or any other formal statement of policy.

This creates a substantial burden on industry, and a barrier to innovation. The device industry is characterized by small, innovative manufacturers that develop new products. In order for these companies to succeed and for their products to come to market, they need to have regulatory predictability and certainty regarding product classification. In creating business plans and strategies, these companies expect that products that are regulated as devices will continue to be regulated as devices, or new products that function similarly to products cleared or approved by FDA as devices will also be regulated by FDA as devices. In the past few years, these expectations have gone unfulfilled, as FDA has chosen to classify some of these newer products (or even new intended uses of products already regulated as devices) as drugs or biologics. In trying to explain its rationale for the disparate treatment of similar products, FDA has drawn, as one court found, "ephemeral distinctions."

These sudden changes in classification have multiple adverse effects. The individual companies find that their plans are balked. Seeking drug approval has profoundly negative effects on the costs of getting to market and the timelines. Seeking redress from FDA can take years as well; FDA's appeal process is not subject to any time limits. The impact of FDA's product classification reversals extends to other companies that are working on their own strategies that learn about these shifts in product classification. This lack of predictability and transparency deters some companies from proceeding or forces them to take steps to gain confirmation of their product's regulatory status, e.g., by submitting Requests for Designation (RFD). Even if the RFD does confirm device status, the company has lost time and money in taking steps to gain regulatory certainty. These measures should not be needed, and yet companies feel compelled to undertake them because they have heard that they cannot rely on how FDA has acted in the past.

FDA needs to address this issue. FDA has acted in an ad hoc manner with multiple classification decisions. There is no final guidance document. FDA did issue a draft guidance in June 2011, which was widely criticized by commenters. The approach that FDA proposed – and had in fact already applied – was questioned by the only federal court to consider this issue. FDA has not issued a new draft guidance or final guidance in the intervening three years. Yet the agency has continued to make classification decisions that depart from prior precedents, using grounds that manufacturers have no means of ascertaining until they find that their product is not a device.

FDA officials themselves would benefit from greater clarity. Companies have entered into extensive discussions with the Center for Devices and Radiological Health (CDRH), only to find out months or years later that the product may not be a device after all. The fact that CDRH officials can have extended discussions with companies about the device regulatory requirements, only to subsequently indicate that the product may not be a device underscores the flaws with the current system.

In considering how to regulate new products, FDA should take into consideration the regulatory classifications set by other countries. The mechanism by which a product functions is independent of geography. Yet FDA has refused to give any weight to product classification decisions in other countries. This leads to anomalous outcomes, where products have entered major global markets as devices, but are deemed drugs – and therefore subject to much more costly and time consuming regulatory requirements – by FDA. FDA has embarked on numerous harmonization projects with other nations, but has steadfastly disregarded regulatory classification decisions elsewhere. While the statutory definitions are not necessarily the same in the United States as in other

countries, the classification decisions by other regulatory bodies can shed useful light on how a globally-marketed product should be regulated. Thus, another way to assist innovative products to enter the United States more rapidly would be if FDA considered the regulatory classification determinations by other countries in making its own regulatory classification determination.

Many device companies based in the United States already introduce their products overseas because of regulatory considerations. FDA's unwillingness to apply those regulatory classification determinations that have been made by other regulatory bodies to companies that then turn to enter the United States market means that many of these products will never be available in this country.

In conclusion, there are many steps that can be taken to enhance innovation. One narrow step that would materially assist multiple companies would be for FDA to establish measures that provide greater clarity – and in appropriate manner – as to whether a new product will be regulated as a device. Having FDA take into consideration the regulatory determinations made by other regulatory bodies would advance certainty, promote global harmonization initiatives, and further encourage innovation.

Sincerely,



Jerry N. Gibbs

Director

Hyman, Phelps & McNamara, P.C.



IDSAs

Infectious Diseases Society of America

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May 30, 2014

Representative Fred Upton
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Representative Diana DeGette
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Submitted electronically to cures@mail.house.gov

RE: 1st White Paper — 21st Century Cures: A Call to Action

Dear Chairman Upton and Ranking Member DeGette:

On behalf of the Infectious Diseases Society of America (IDSAs), thank you for launching the 21st Century Cures Initiative and providing us with this opportunity to comment. We share your commitment to fostering the development of desperately needed new diagnostic tools and treatments (especially antibiotics) to combat infectious diseases, and hope that the recommendations we share below will help you craft meaningful, life-saving policy solutions.

Antibiotics are generally accepted as the greatest curative development of the 20th century and now credited with a 26 year increase in average longevity. This progress is threatened by the rapid rise of antibiotic-resistant bacteria coupled with a persistent market failure to develop new antibiotics. This public health crisis has been well documented by the Centers for Disease Control and Prevention, the World Health Organization and multiple other government entities and non-government experts, including IDSAs with our [2004 Bad Bugs, No Drugs report](#) and our [2011 Combating Antimicrobial Resistance: Policy Recommendations to Save Lives report](#). We are on the very real, very frightening precipice of a post-antibiotic era.

IDSAs is advocating for new antibiotics and diagnostics to improve and save the lives of the many patients who are suffering from serious or life-threatening infections, patients like [Addie Rerecich](#). Addie was a healthy 11-year-old girl from Tucson, AZ, who contracted an infection which was not promptly diagnosed. The infection spread to her lungs and throughout her body and was resistant to nearly every antibiotic doctors tried, except for one last resort: a highly toxic antibiotic. As a result of this serious infection, Addie endured a months-long hospital stay, double lung transplant, significant physical therapy and healthcare costs of over \$6 million.

We lack antibiotics to safely and effectively treat patients like Addie for a variety of reasons. Unlike other types of drugs, the use of antibiotics decreases their effectiveness over time due to the development of resistance by the bacteria that infect us. And companies are lacking sufficient incentives to develop new antibiotics. Antibiotics are typically priced low compared to other new drugs, used

for a short duration, and held in reserve to protect their utility, making them far less economically viable investments for companies than other types of drugs. In 1990, there were nearly 20 pharmaceutical companies with large antibiotic research and development (R&D) programs. Today, there are only 2 or 3 large companies with strong and active programs and a few small companies with more limited programs. An [IDSA report](#) issued in April 2013 identified only seven new drugs in the development pipeline for the treatment of serious infections caused by multidrug-resistant Gram-negative bacilli.

IDSA's 2013 [Better Tests, Better Care](#) report calls attention to the equally urgent need for new infectious diseases diagnostic tests that provide rapid results, are easy to use, and accurately identify the pathogen causing an infection and the best antibiotic to use. New and improved diagnostics can significantly improve patient care by giving physicians the information they need to more rapidly provide appropriate treatment. Currently, 20-30% of patients with sepsis receive inadequate initial treatment because the cause of the disease can take several days to diagnose. Better diagnostics can also improve public health by identifying patients for whom isolation or other infection control measures are needed, improving the tracking of outbreaks and emerging infectious disease threats. Improved diagnostics can also guide the appropriate use of antimicrobial drugs, and therefore are critical to the campaign to address antibiotic resistance. Thanks to advancements in scientific research, promising new diagnostic tools are within reach. For example, new diagnostics may be able to provide rapid results, screen for multiple pathogens at once, and even detect non-culturable organisms. But greater investment and improved regulatory policies are needed to ensure that scientific advancements translate into the development and use of new diagnostics.

IDSA continues to advocate for a well-coordinated, multi-pronged effort with strong federal leadership that is inclusive of all stakeholders to address antibiotic resistance and the need for new antibiotics and diagnostics. We appreciate that the Committee recognizes that the federal government must set policies as well as provide resources necessary to optimally engage the knowledge and capabilities found in academia and industry. While the Generating Antibiotic Incentives Now (GAIN) Act provisions in the FDA Safety and Innovation Act (FDASIA) were an important first step, key stakeholders agree that additional incentives will be necessary to help foster the development of needed new antibiotics and diagnostics.

While global research and discovery is a positive development, the U.S. must maintain its leadership role. How can we make sure that is the case? How much of the contributions should come from public and private sources? How can public-private partnerships further the discovery process?

The Committee has recognized that the U.S. must act to spur antibiotic research & development and in 2012, led an important first step by advancing the GAIN Act. Despite that important progress, the U.S. continues to lag behind the European Union (EU) with regard to incentivizing antibiotic and diagnostic development.

In 2011, the EC launched the Rapid Point-of-care test Platforms for Infectious Diseases (RAPP-ID) project, another PPP bringing together government experts, academia and industry, which

aims to develop fast and reliable point-of-care tests for the detection of various pathogens. RAPP-ID is gathering input from clinicians to focus its activities on areas of greatest need that can most significantly impact patient care. This effort is focused on diagnostics for blood infections, lower respiratory tract infections (including community-acquired pneumonia and ventilator-associated pneumonia) and tuberculosis.

In 2012, the European Commission (EC) launched their ground-breaking New Drugs For Bad Bugs (ND4BB) public private partnership (PPP). PPPs are essential to furthering the discovery process for new antibiotics because they convene the required diverse stakeholders to tackle the complex scientific and economic challenges facing antibiotic R&D. For example, ND4BB brings together government leaders, academia, industry and other experts for an unprecedented sharing of information and multi-disciplinary collaboration. The focus of the overall program is to develop better networks of researchers, create fluid and innovative clinical trial designs and provide incentives for companies to meet the challenges of antibiotic resistance quickly and efficiently. Initial funding for ND4BB (approximately \$300 million for the first phase) was nearly equally split between government and industry sources.

The US has begun recognizing the importance of PPPs for antibiotic and diagnostic development, though US efforts have been much more limited in scope than EU activities. For example, the Biomedical Advanced Research and Development Authority (BARDA) has become a critical source of funding for companies developing novel antibiotics and diagnostics. However, discreet projects, while valuable, will likely not yield as powerful an impact as a large-scale, well-coordinated PPP similar to the ND4BB and RAPP-ID initiatives.

IDSA urges US government leaders to establish a large scale PPP, similar to the European effort, to ensure that we do not continue falling further behind. Industry leaders at the forefront of ND4BB and RAPP-ID have noted that government initiative was vital to the creation of these valuable partnerships.

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

Please see the above answer regarding how the EU is utilizing groundbreaking public private partnerships (PPPs) to tackle the challenges facing antibiotic and diagnostic development.

In the U.S., investigators and developers face several challenges that can impede the research, development or approval of a new diagnostic test. Current overly broad conflict of interest policies impede expert participation in company advisory boards or expert panels. For example, many Food and Drug Administration (FDA) advisory panel expert positions remain vacant due to conflict of interest policies, hindering the ability of these panels to carry out their objectives. These policies also impact the ability of companies to obtain independent validation of pioneering diagnostics. Laboratories that are compensated for testing these new methods are subject to conflict of interest policies, excluding much needed expertise to the validation process.

We urge the Committee to work with the FDA toward revisions of these policies that would protect against legitimate conflicts of interest but still allow access to key experts needed for product design and development. PPPs, as discussed above, should also be encouraged, as they provide an external, less conflicted foundation that also expedites drug and diagnostics development.

We must also avoid adding further regulatory burden to research. [IDSA has expressed concern](#) that the recent Health and Human Services (HHS) proposed rule “Strengthening Consent Protections Related to Reuse or Additional Analysis of Existing Data and Biospecimens,” would add undue burden by forcing researchers to obtain written consent for the reuse of de-identified clinical samples. Diagnostic development relies heavily on the use of clinical samples that are collected during routine standard of care and anonymized. A large number of samples from patients with varying characteristics (e.g., age, clinical condition, clinical setting) are needed to ensure that test results more accurately reflect a real-world patient population. Requiring informed consent for reuse of deidentified specimens would add considerable time and expense to studies, limiting the diversity of patient populations and the types of pathogens detected in studies.

The timelines, size, failure rates, and costs of conducting trials are at all-time highs, with administrative and regulatory burdens often contributing to such increases. What can be done to help reverse these trends?

Clinical trials for antibacterial and antifungal drugs to treat serious or life-threatening infections face significant challenges. Some of the most dangerous pathogens are to date occurring in relatively small numbers of patients, making it difficult to impossible to populate traditional, large scale clinical trials. It is important to develop drugs to treat infections caused by these deadly pathogens before they infect larger numbers of people. Moreover, when a pathogen is resistant to all approved antibiotics, there is no effective antibiotic against which to compare the new antibiotic, which is the standard procedure for clinical trials. Compounding the problem is the lack of rapid diagnostic tests to identify patients infected with certain pathogens who may be eligible for antibiotic or antifungal clinical trials.

IDSA urges the Committee to act upon the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, which would help address some of these serious regulatory hurdles by creating a new FDA approval pathway in which companies could study new antibacterial or antifungal drugs to treat serious or life-threatening infections for which there is an unmet medical need in smaller clinical trials and receive approval for the limited population in most need of the therapy.

The ADAPT Act would speed patient access to desperately needed, life-saving new drugs, and it includes important provisions to help guide the appropriate use of these drugs. IDSA recommends that one additional provision be added to require a prominent and conspicuous visual element, such as a logo, on the labeling of drugs approved under this new pathway to make it as simple as possible for the health care community to easily recognize that these drugs

have been approved in a different manner than traditional antibiotics and must be used appropriately.

We are pleased that the ADAPT Act has garnered broad bipartisan support among Committee members. [Numerous medical societies and public health organizations](#) share IDSA's view of this important legislation. As the Committee heard during its recent hearing, the President's Council of Advisors for Science and Technology (PCAST) endorsed this approach to antibiotic development in its 2012 report.

A key challenge in clinical trials for new diagnostics is access to clinical samples containing rare pathogens. Many clinical laboratories no longer freeze specimens containing novel or unusual organisms for further use. Even when such critical samples are available, the cost of accessing samples has, in many cases, become prohibitive. The formation of centralized, well indexed biorepositories would significantly ease the clinical trials process. This approach has been recommended in recent reports from the Transatlantic Task Force on Antimicrobial Resistance, and the Center for Health Security at the University of Pittsburgh Medical Center. **IDSA recommends that the Committee, in conjunction with the FDA and NIAID, explore the best way to establish such biorepositories, taking into account the need for standardized protocols for collection and storage of specimens.** IDSA recognizes that establishing and maintaining such biorepositories will require financial support, and we suggest that companies and researchers who wish to access the specimens would be required to pay a fee to support the biorepositories. For more information, IDSA has developed a brief [proposed prototype](#) for establishment of an infectious diseases clinical specimen repository.

FDA's active participation in partnerships like the Biomarkers Consortium, the Critical Path Initiative, and the Clinical Trials Transformation Initiative is critically important. How can these types of trials become the norm? Is there a better way to validate biomarkers and surrogate endpoints? What roles can NIH and other outside experts play in the process? What cultural or organizational issues must be addressed in order to effectuate these broader changes?

IDSA members have participated in the Foundation for the NIH (FNIH) Biomarkers Consortium's efforts to develop new endpoints for trials of antibacterial drugs — an effort that was initiated at FDA's request. Although overall IDSA agrees with the Committee that “much progress remains until efficient trials...are no longer the exception to the rule,” we note that much progress has been made recently.

In 2010, the Biomarkers Consortium began to address the lack of readily quantifiable, reproducible, externally verifiable and feasible endpoints for modern clinical trials in community-acquired bacterial pneumonia and acute skin infections. The FNIH convened scientists from across academia, government, and industry to develop an historic consensus on new trial endpoints. These new endpoints have already played a role in the approval of one new antibacterial drug (ceftaroline fosamil). The FNIH project team is currently developing and validating additional specific outcome measures to support future clinical trials in these

infections. In addition, the FDA has incorporated the Biomarkers Consortium's recommendations into regulatory guidances.

FDA again approached the Biomarkers Consortium for assistance with evaluating new endpoints for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). These difficult-to-treat, increasingly drug-resistant infections cause high morbidity and mortality. Progress on clinical trial endpoints to allow the development of novel antibacterial treatments is essential. The FNIH project team has already submitted to the FDA a set of interim considerations for design and conduct of clinical trials in these indications; a number of the FNIH conclusions now appear in a recently issued FDA draft guidance.

IDSA members have also participated in the Clinical Trials Transformation Initiative (CTTI), which was established by Duke University and the FDA as a public-private partnership in 2007 and now comprises over 60 member organizations engaging patients and experts to facilitate discussion of current practices and challenges in the design and conduct of antibiotic trials and to develop novel approaches to overcome these challenges. CTTI's work focuses in three areas:

1. **HABP/VABP:** CTTI is developing recommendations on alternate study design elements to overcome barriers to research. To accelerate the study process, CTTI is generating a prototype study protocol that could be less burdensome to investigators and patients and reduce inefficiencies and costs of drug development. CTTI facilitated the creation of a [pilot network that is being further developed through NIAID](#) funding. CTTI continues to focus on streamlining protocol elements, as well as seeking practical, more efficient approaches for data collection and operational processes.
2. **Unmet Need:** CTTI is identifying and assessing new approaches for weighing the benefits, risks, and uncertainties of potential new antibacterial drugs in unmet need situations. Patients' and caregivers' tolerance for risk and willingness to be treated with drugs approved through non-traditional trials will be explored.
3. **Pediatric Populations:** CTTI will identify best practices and recommendations on how industry might comply with the Pediatric Research Equity Act (PREA) recommendations for anti-infective drugs. CTTI will facilitate development of new antibacterial drugs and advance the knowledge for conducting successful trials in pediatric populations.

Taken together, the evidence and consensus building through the FNIH Biomarkers Consortium, CTTI and other public private partnerships will contribute to simplifying and speeding up the clinical study process for antibiotic development in areas of critical, unmet medical need. **The Committee should continue encouraging FDA to remain engaged with these entities and to rapidly adopt their findings and recommendations into improved clinical trial guidances.**

Are there areas or opportunities where the agency is not using these authorities to their maximum potential where it should be? Is FDA structured and managed to enable the agency to rapidly incorporate innovative new approaches and technologies into its review processes?

How can Congress ensure that the regulatory science keeps pace with advances in personalized medicine, including diagnostics?

While the FDA has taken promising first steps, further action is needed to reduce regulatory burden for the development and approval of new diagnostics. Currently, innovative diagnostic tests must use the FDA Premarket approval (PMA) pathway for regulatory approval. This route, unlike the 510(k) pathway for the modification of previous tests, requires additional clinical trials that are often cost-prohibitive. The FDA should streamline the PMA process by shifting some review for devices to the postmarket phase. The FDA Center for Devices and Radiological Health's (CDRH) recently released draft guidance document, "[Expedited Access PMA for Unmet Medical Needs for Life Threatening or Irreversibly Debilitating Diseases or Conditions](#)," represents a good first step for speeding patient access to urgently needed diagnostics for some of the most dangerous infections.

As new diagnostic tests are brought to the market, they often outpace the current procedural terminology (CPT) reimbursement code system relied upon by Medicare. In many cases, reimbursement does not even fully cover the cost of using a test. This situation serves as a disincentive to diagnostics R&D and severely hampers the widespread clinical adoption of diagnostics. We appreciate the "Protecting Access to Medicare Act of 2014" (P.L. 113-93), which includes multiple provisions to improve diagnostic reimbursement. **We urge the Committee to engage in oversight on this issue to ensure that the Centers for Medicare and Medicaid Services (CMS) effectively and appropriately implements these new policies.**

Are the economic incentives and policies currently in place sufficient to encourage robust investment and promote innovation? How can we make sure that biomedical research and product development continues and attracts venture capital?

Current financial incentives for antibiotics and diagnostics R&D, including the GAIN Act and research funding through multiple federal agencies, are important down payments for these priorities, but more work remains to be done, including greater support for the NIAID Antibacterial Resistance Leadership Group ([ARLG](#)), improved reimbursement for antibiotics, tax credits to stimulate antibiotic and diagnostics R&D, and stronger funding for several agencies that support these efforts.

NIAID recently established the ARLG to develop, design, implement, and manage a clinical research agenda to increase knowledge of antibacterial resistance. The ARLG will focus on antibacterial drug and diagnostic development, optimal usage strategies, infection control and activities to limit the development of resistance. **As called for in Section 5 of the [Strategies to Address Antimicrobial Resistance \(STAAR\) Act, H.R. 2285](#), the House Energy & Commerce Committee should formally authorize the ARLG to provide statutory foundation to NIAID's commitment to implement a comprehensive research agenda.** If properly supported, the ARLG is well poised to help catalyze efforts to bring new antibiotics and diagnostics to patients.

IDSA urges you to improve the economic environment that fosters biomedical innovation and recognizes this effort may include collaborative work with colleagues on other committees (particularly Ways & Means and Appropriations). For example, as noted above, IDSA applauds Congress for recently improving reimbursement for diagnostics through the SGR patch bill. Reimbursement mechanisms should also be used to help stimulate antibiotic R&D, such as through the [Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms \(DISARM\) Act, H.R. 4187](#). The bill would provide Medicare add-on payments for antibiotics used in inpatient settings to treat infections associated with high rates of mortality and that address an unmet medical need. Strong communication between CMS and FDA is critical for the success of such efforts, to help ensure that criteria to determine a drug's coverage and payment are applied in a scientifically appropriate and consistent manner that provides companies with the certainty and predictability they need in order to develop life-saving new antibiotics.

IDSA is also working on proposals for targeted and transferrable R&D tax credits to further stimulate antibiotic, antifungal and rapid infectious diseases diagnostics R&D, and hopes the Committee will collaborate with other committees to include such tax credits as a complimentary provision to the 21st Century Cures Initiative. While the GAIN Act and DISARM Act provide valuable incentives, companies must fully develop a product before receiving the benefits from increased exclusivity or reimbursement. Economic modeling has indicated that financial support during expensive clinical trials, as provided through tax credits, would be a powerful incentive to complement enhanced exclusivity and reimbursement. In fact, Ernst & Young analysis estimated that our tax credit proposal would result in an additional 5-7 new antibiotics or antifungal drugs to treat serious or life-threatening infections in the pipeline every year.

Lastly, IDSA supports increased direct federal funding to spur innovation through NIAID, the BARDA, the Centers for Disease Control and Prevention (CDC), the Defense Threat Reduction Agency (DTRA), and the Defense Advanced Research Projects Agency (DARPA). IDSA urges the Committee to conduct oversight, where appropriate, to ensure that NIAID is appropriately targeting resources for the most urgent diagnostics needs. For example, NIAID should work to ensure that the peer review process for diagnostics grant submissions includes study sections with appropriate expertise to evaluate feasibility and clinical applicability, as well as scientific merit. The NIAID Small Business Innovation Research (SBIR) program is an important source of funding for diagnostics research, and additional resources would expand this program's impact. The ARLG, mentioned above, should also receive additional funding to further its research. IDSA also encourages increased funding for BARDA to further R&D of medical countermeasures, including antibiotics and diagnostics for both intentional attacks and naturally emerging infections. Finally, IDSA encourages Congress to be mindful of CDC's role in research and innovation and provide the agency with strong funding. For example, CDC's proposed [Detect and Protect Against Antibiotic Resistance initiative](#) – which has [broad support](#) – includes the establishment of a bacterial isolate library that could be useful to researchers and companies for the development of new antibiotics and diagnostics.

What else can be done to foster continued learning and investment in research after a drug or device, or combination thereof, has initial FDA approval? How can electronic health records and other health information technologies play a role? What uncertainties or barriers currently exist in post-market, real world delivery settings—legal, regulatory, commercial, or otherwise—and how should they be addressed? There are reports that diagnostic testing breakthroughs sit unrealized due to regulatory uncertainty and other market forces that deter translating such innovation into patient-centered solutions. What are the current barriers to bringing new testing discoveries to market, and how might we overcome them?

After a new antimicrobial drug is approved, it is critical to monitor its use and make these data publicly available. Monitoring can provide physicians with important information regarding the drug's effectiveness and side effects, which can help strengthen patient care.

The CDC's National Healthcare Safety Network (NHSN) currently collects data on antimicrobial drug use. However, healthcare facility participation is voluntary and only a small number of healthcare facilities currently report these data. **The Committee should explore mechanisms to incentivize or facilitate broader participation in NHSN.** It is also notable that NHSN has received flat funding for the last several years, despite repeated requests by the Administration for funding increases. **IDSA continues to support increased funding for NHSN and urges the Committee to work with its colleagues on the Appropriations Committee as well as CDC to strengthen support for NHSN and consider whether additional authorizing language would be helpful to increase reporting of critical antibiotic use and resistance data.**

IDSA also urges the Committee to advance the STAAR Act, mentioned above, which would strengthen antimicrobial drug use data collection. The STAAR Act directs CDC to work with private vendors, health care organizations, pharmacy benefit managers and other entities to obtain reliable human antimicrobial drug consumption data and to publicly report these data. The bill also directs the Office of the National Coordinator for Health Information Technology to work with CDC to determine how best antimicrobial use and resistance data can be incorporated into meaningful use reporting.

Additional research is also needed to understand more fully the impact of diagnostics. While we recognize that innovative infectious diseases diagnostic tests can have a significant impact on patient outcomes, public health, and healthcare resources utilization, we lack concrete data to inform and demonstrate these points. **We urge the Committee to explore ways to encourage the conduct of outcomes research to provide data on diagnostic use in varied clinical settings and the effect of diagnostic testing on patients, public health and the healthcare system.** With strong supporting data, clinicians can be educated about the utility and optimal use of new tests, increasing the rate of adoption and appropriate use in the healthcare community. The Patient Centered Outcomes Research Institute (PCORI) is well positioned to support evaluation of clinical outcomes of new diagnostics, but to date PCORI has focused largely on chronic conditions rather than infectious diseases.

Again, IDSA thanks you for launching the 21st Century Cures Initiative and for providing this opportunity for comment. The Society stands ready to assist you in advancing this important initiative, answering any additional questions that you have and providing any additional information that may be helpful. As a next step, attached please find a listing of IDSA experts that we would be happy to provide for future hearings, roundtables or other discussions. To connect with any of these experts, or to request any additional information on IDSA's recommendations, please contact [REDACTED], IDSA's Director of Government Relations, at [REDACTED]

Sincerely,

[REDACTED]

Barbara E. Murray, MD, FIDSA
President, IDSA

Attachment: IDSA Experts on Selected Issues

Helen W. Boucher, MD, FIDSA
IDSA Board of Directors
Director, Infectious Diseases Fellowship Program
Associate Professor of Medicine
Division of Geographic Medicine and Infectious Diseases
Tufts Medical Center
Areas of policy expertise:
Antibiotic Research & Development (general)
Antibiotic Clinical Trials Issues
Antibiotic Economic Incentives
Public Private Partnerships

Angela M. Caliendo, MD, PhD, FIDSA
Chair, IDSA Diagnostics Task Force
Executive Vice Chair, Department of Medicine
Chief, Division of General Internal Medicine
Brown University Alpert Medical School
Areas of policy expertise:
Diagnostics Research & Development

Karen C. Carroll, MD, FIDSA
Member, IDSA Diagnostics Task Force
Professor of Pathology and Medicine
Director, Division of Medical Microbiology
Director, Medical Microbiology Fellowship Program
The Johns Hopkins University School of Medicine
Areas of policy expertise:
Diagnostics Research & Development

Henry F. "Chip" Chambers, MD, FIDSA
Chair, IDSA Antimicrobial Resistance Committee
Professor of Medicine
Director, Clinical Research Services
University of California San Francisco Clinical and Translational Sciences Institute
Areas of policy expertise:
Antibiotic Research & Development (general)
Antibiotic Clinical Trials Issues
Antibiotic Economic Incentives

Barbara E. Murray, MD, FIDSA
President, IDSA
J. Ralph Meadows Professor
Director, Division of Infectious Diseases
University of Texas Health Science Center
Areas of policy expertise:
Antibiotic Research & Development (general)
Diagnostics Research & Development (general)

May 30, 2014

The Honorable Fred Upton
Chairman
House Energy & Commerce Committee
2183 Rayburn HOB
Washington, DC 20515

The Honorable Diana DeGette
Member
House Energy & Commerce Committee
2368 Rayburn HOB
Washington, DC 20515

Dear Chairman Upton and Congresswoman DeGette:

The Leukemia and Lymphoma Society (LLS) appreciates this opportunity to comment on the *21st Century Cures: A Call to Action* whitepaper. As the world's largest voluntary health agency dedicated to the needs of blood cancer patients, LLS is a strong supporter of action that will facilitate the discovery, development and delivery of new, safe, and effective therapies for blood cancer patients. Each year more than 140,000 Americans are newly diagnosed with blood cancers, accounting for nearly 10 percent of all new cancer diagnoses in the United States. Our mission is to find cures for leukemia, lymphoma, and multiple myeloma and to ensure that blood cancer patients have sustainable access to quality, affordable, and coordinated healthcare.

The efforts of the 21st Century Cures initiative are well timed given the advances in our understanding and treatment of blood cancer and other diseases over the past decade. We are grateful for the opportunity to comment, and request that you continue to actively engage the patient community to ensure that the development of cures takes into account the risk/benefit tolerance of patients at the earliest stages. LLS is a significant stakeholder in the drug and device development process, and has provided more than \$1 billion for research aimed at discovering, developing and delivering blood cancer cures since its founding. LLS-funded research has been part of nearly all of the FDA-approved therapies for blood cancer treatment.

Given our position both as a patient advocacy group and as a funder of clinical research, we understand the close relationship between the discovery and development of new cures and the life-changing effects that these therapies have on patients' lives. However, there are still significant patient concerns that must be protected throughout the drug development process, and any Call to Action must ensure that patient voices are heard.

The creation of the breakthrough therapy designation and expansion of the accelerated approval program included in FDASIA were an important step to provide robust access to new cures and therapies, but there is still significant work to be done to guarantee that new cures are being discovered, developed, and delivered for our nation and the world.

LLS respectfully submits the following policy recommendations to the Committee for consideration:

- Develop policies that prevent abandonment of promising early-stage research due to inadequate funding, and ensure policies that adequately fund all stages of research, including the translational sciences.
- Promote a flexible drug development process to keep pace with the evolution of scientific discoveries.
- Adopt policies that ensure that once approved, patients have access to necessary, life-saving therapies.

Discovery:

LLS recommends that the Committee develop policies that prevent abandonment of promising early-stage research due to inadequate funding. Persistent cuts to NIH and other research funding have stalled innovation and delayed or destroyed the potential development of countless new therapies and cures in the research pipeline. Promising research should not be abandoned in the research pipeline, and funding should be more widely available so that scientists are in the lab making new discoveries rather than competing for grants. As with research into the basic causes of disease, the financial incentives for industry investment into early stage-research are often not favorable. LLS is seeking to help fill this gap, and to prevent the abandonment of research that displays promise but lacks financial support.

The Federal Government, in partnership with academic institutions, industry and patient groups like LLS, plays a critical role in funding and supporting the basic scientific discoveries. These fundamental discoveries become foundational scientific building blocks used to construct the next generation of therapies and cures. Creating a sustainable and properly resourced public funding mechanism, along with continuing investment from the private sector, will broaden the breadth and depth of scientific knowledge to facilitate the development of new therapies and cures.

Restoring adequate funding to the National Institutes of Health (NIH) and its individual research centers should be a top priority for the Congress and the Administration. As NIH Director Dr. Francis Collins stated during the 21st Century Cures Roundtable held on May 6, 2014, recent reductions in funding as a result of inflation, stagnant appropriations, and sequestration have greatly diminished the NIH's ability to unearth new scientific discoveries. Furthermore, the lack of funding for research will have long lasting effects. Congress successfully provided some relief in the Gabriella Miller Kids First Research Act (GMKFRA), which LLS endorsed. Targeted funding like the GMKFRA is a step in the right direction, but is insufficient to restore funding to adequate levels. The 21st Century Cures initiative should inject increased funds into the NIH in a strategic manner to promote promising research at early stages. .

As with many other complex diseases, we still do not understand the cause of blood cancers, and have no known methods of prevention or screening. The private sector plays an important role in funding research in this area, but more research and collaboration is needed.

One example is the LLS initiative entitled Beat AML¹. AML, or Acute Myeloid Leukemia, is a disease that causes more than 10,000 American deaths each year, and where little research progress has been made over the past thirty years. Beat AML is a multi-institution research initiative designed to unlock the underlying genetic causes of AML, and leverage the advances in personalized medicine to accelerate findings and improve outcomes for AML patients. LLS has committed \$8.2 million to the initial three-year project that will collect treatment data from more than 900 patients. With our partners, we intend to use multiple state-of-the-art technologies (genomics, etc.) to comprehensively identify gene mutations and other abnormalities, and to help develop targeted drugs for AML therapies and select appropriate targeted therapies for individual patients. We believe that Beat AML can serve as a model for research in other areas and would be happy to discuss how to build on initiatives like Beat AML with the Committee.

¹ For more information, see: http://www.lls.org/#/aboutlls/news/newsreleases/09162013_lls_and_ohsu_launch_beat_aml

Finally, the Committee should ensure policies that adequately fund all stages of research, but pay special attention to those that promote translational science research. Translational science is essential to the development of new cures, because it bridges the gap between basic scientific discoveries and applied treatments. The National Center for the Advancement of Translational Science (NCATS) at the NIH catalyzes the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics. Recently, LLS formed *The Learning Collaborative*, a partnership between NCATS, the University of Kansas Medical Center and the NIH with the goal of bringing drug discovery and drug development expertise together with funds from multiple sources to make advances in blood cancer treatment. This partnership produced an early breakthrough when it discovered that the existing arthritis drug Auranofin could be repurposed and used in the treatment of Chronic Lymphocytic Leukemia. Translational science is particularly cost-effective because it leverages the existing field of scientific knowledge for promising new applications.

Major gaps in funding exist at all stages of the discovery process. Although LLS and other private stakeholders have developed innovative programs that attempt to fill the gaps, the overarching economic incentives create an environment where a shortage of federal funds will lead to a shortage of scientific discoveries. Adequately funding the discovery process is essential to keeping the United States at the forefront of biomedical innovation.

Development:

To ensure the continued development of new therapies, the Committee must promote a flexible drug development process to keep pace with the evolution of scientific discoveries. Advances in personalized medicine have discovered treatment regimens based on combinations of drugs, rendering the current clinical trials and regulatory approval process outdated for cancer patients.

LLS promotes the development of new cures for blood cancer through its Therapy Acceleration Program (TAP), which provides funding for promising blood cancer therapy development projects. TAP looks to fund projects related to therapies that have the potential to change the standard of care for patients with blood cancer, particularly in areas of high unmet medical need.

TAP employs multiple strategies to speed the development of blood cancer treatments and supportive diagnostics, partnering with academic institutions and biotech companies to develop and invest in promising new treatments for our patients. TAP plays a critical role in ensuring the development of new cures, and in fertilizing the blood cancer drug development pipeline. We encourage the Committee to look into TAP as a potential model for further ways that the federal government can create and foster partnerships throughout the drug development process.

Despite the advances made in research, one of the major impediments to drug development is cost. Current estimates to bring a drug to market top \$1 billion. A large portion of that investment is the cost associated with populating and conducting clinical trials. Trials must be smaller, faster and less expensive to alleviate the financial strain on innovation. This will require the FDA, along with providers, patients, and researchers, to develop and agree upon new trial designs and endpoints. As the Committee has noted, many advances in cancer care are based upon targeted and precision therapies that make the current Phase I-III clinical trial system unrealistic for small and rare disease populations. The Committee should continue to build on

important initiatives that accelerate innovation and provide incentives to develop drugs used in rare disease populations like the Orphan Drug Act, the breakthrough therapy designation, and the accelerated approval program to target resources most efficiently at the FDA and in industry. Special consideration in revamping the clinical trial paradigm should be given to new targeted and specialized therapy regimes in the cancer space. Facilitating innovation in this space could be a primary driver to curing cancer, and lowering costs to the healthcare system.

A new clinical trials paradigm should explore multi-company and multi-drug trials. Current research shows that the promise of curing cancer lies largely in combination drug therapies targeted at certain genetic markers. The evolving regulatory landscape must account for these types of trials and companies should be encouraged to participate in these trials, as drugs with limited effectiveness when tested alone may be part of a larger drug regimen with far greater impact.

Another desirable characteristic of reform would be to further promote the use of adaptive clinical trial design which permits sponsors to adapt and make revisions to their clinical trial design as they receive data on the trial's progress in real time. The FDA also needs the tools to take advantage of the ever increasing amount of data available to the research public, and to the extent possible share the data it collects in an effort to make clinical trials more efficient. Finally, the Committee must encourage the FDA to clarify through guidance the validation of biomarkers and surrogate endpoints to ensure that regulatory science keeps pace with scientific development.

Delivery:

New cures and therapies are only beneficial if they are widely available to the intended patient population. For new therapies, gaining FDA approval is just the first hurdle to ensure that patients are able to access the therapy. After the FDA has cleared a product, drug sponsors and innovators seek reimbursement through public and private payers. Payer review of therapies is in effect a second review process that duplicates much of the FDA review, but may require manufacturers to submit additional clinical studies to demonstrate a product's superiority or equivalency to the existing market alternatives. The reimbursement review process can further delay the delivery of treatment to patients, and create additional scientific requirements that need to be addressed before a therapy becomes widely available for use in patients.

Blood cancer patients are particularly susceptible to practices that can place their drugs beyond the patient's financial grasp. The increased use of specialty tiers by plan designs in the private and public sector, combined with cost-sharing requirements based on co-insurance rather than fixed co-payments place financial strain on families, and may even cause patients to choose between life-saving therapies and other basic necessities. Due to the evolving and complex nature of cancer care, new blood cancer therapeutics are placed on a specialty tier. Congress can solve this critical patient access issue by including HR 460, the Patients Access to Treatments Act of 2013 introduced by Congressman McKinley and Congresswoman Capps in any legislation it produces. The bill would provide more affordable prescriptions in the commercial health insurance market. To alleviate access barriers created by specialty tier in the Medicare Part D prescription drug benefit, the Committee should include HR 2827, the Part D Beneficiary Appeals Fairness Act, which would allow beneficiaries to appeal the placement of their drug on a specialty tier.

Similarly, many of the innovative blood cancer therapies being produced today are oral agents, rather than traditional chemotherapies delivered through an IV. Traditional therapies are frequently covered under a plan's medical benefit, which often has lower cost-sharing requirements than a health plan's pharmacy benefit. Much like specialty tiers mentioned above, plans that employ a cost-sharing requirement incorporating a coinsurance payment can result in catastrophic results for patients. HR 1801, the Cancer Drug Coverage Parity Act of 2013 represents an important opportunity for the Committee to address this problem at the national level. Over half of the states have enacted laws that require oral parity for cancer drugs, and the Committee should include the bill in any final legislation it produces.

Delivery of new cures also includes tracking their impact on patient's lives. The Committee should continue to support initiatives to garner more patient and treatment data to identify potential new cures and treatment pathways. One mechanism to accomplish this is to incentivize the use of patient data registries. The use of clinical registries is already common in CMS initiatives like the Physician Quality Reporting System. The Committee should build on this groundwork and seek to develop policies that incentivize greater participation in registries by patients and providers. LLS is committed to understanding both the life cycle of blood cancer and its treatment. To that end, we have partnered with the Cancer Support Community (CSC) to develop a cancer experience registry that will capture all treatment information including tracking variables in cancer care that go beyond the clinical efficacy of treatment like side effects management, cancer care planning, financial concerns and the emotional and social effects of cancer experiences.

Conclusion

We appreciate the Committee's interest in producing a regulatory environment that will maintain America's position as the leader in biomedical innovation. Discovering, Developing and Delivering new treatments to patients with blood cancers is central to the LLS mission and we applaud the Committee for proactively undertaking the 21st Century Cures initiative to improve these processes across the entire biomedical industry.

Please do not hesitate to contact me at [REDACTED] should you or your staff have any questions.

Sincerely,

[REDACTED]
Brian Rosen
Senior Vice President, Public Policy
The Leukemia & Lymphoma Society



National
Kidney
Foundation™

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New York, NY 10016

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www.kidney.org

May 30, 2014

Chairman Fred Upton & Representative Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Re: 21st Century Cures: A Call to Action

Dear Chairman Upton and Representative DeGette,

The National Kidney Foundation appreciates the opportunity to submit comments on the House Energy and Commerce Committee's 21st Century Cures Call to Action. NKF is America's largest and oldest health organization dedicated to the awareness, prevention, and treatment of kidney disease for hundreds of thousands of healthcare professionals, millions of patients and their families, and tens of millions of people at risk. In addition, NKF has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD), since 1997 through the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI).

An estimated 26 million people have Chronic Kidney Disease and another 73 million are at risk. This is a substantial public health problem, yet it gets far less attention and resources than the scope of the problem warrants. The leading causes of CKD are diabetes and hypertension. However, there are also genetic and other lesser known causes of kidney disease such as glomerulonephritis, polycystic kidney disease, Alport Syndrome, IgA nephropathy, among others. Kidney disease is a progressive disease and is often asymptomatic until the later stages. People with kidney disease are at greater risk of cardiovascular events, acute kidney injury, and end-stage renal disease (ESRD). There is no cure for kidney disease or its causes. Dietary changes, blood pressure management, and avoidance of certain medications can slow the progression and, for some, avoid kidney failure all together, but many people are not diagnosed or aware of their kidney disease until it has progressed to kidney failure. Thanks to the Medicare ESRD benefit most people with kidney failure qualify for Medicare coverage, regardless of their age, providing them better access to a dialysis or transplant. However, Medicare spends 34.3 billion dollars, 6.3 percent of the Medicare budget on a

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population that accounts for 1% of Medicare beneficiaries.¹ It is imperative that this country focus on CKD upstream to prevent ESRD and that more efficient and effective treatments for kidney failure are brought to market.

In addition to the challenge of recruiting for clinical trials, due to the fact that most people are unaware they have kidney disease in its earlier stage, one of the greatest barriers to getting cures and treatments to prevent progression of kidney disease to kidney failure is the time it takes to complete those trials. Currently the FDA uses a doubling of serum creatinine (57% decline in kidney function based on glomerular filtration rate) as an endpoint in clinical trials to receive FDA approval, but the trial design required to reach that endpoint can take well over five years and cost billions of dollars, making studies in CKD drugs less attractive to manufacturers. In December 2012, NKF and the FDA cohosted a workshop to discuss potential surrogate endpoints for clinical trials. In preparation for the workshop an extensive data analysis was completed and then presented during the workshop. The attendees, who included experts in clinical research, epidemiology and FDA representatives, concluded that in some kidney disease populations a 30 or 40% decline in kidney function was adequate to show a high risk of mortality and progression to ESRD. The FDA is now considering these new endpoints for pivotal research trials in specific kidney disease populations, but would like to see additional research to confirm the findings prior to widespread use in clinical development programs.

Additionally greater investment in research could help answer some of the questions we still do not know. For, example we still need to better understand why some people with CKD progress and others do not or progress more slowly. NKF in partnership with John Hopkins runs a global CKD Prognosis Consortium, which has data on 1.7 million people with CKD in 35 cohorts to help answer some of the unknown questions of CKD. Great work is also being done on some of these answers at NIH, but the scope and resources allocated are inadequate given the significant public health issue kidney disease poses. More federal funding for kidney disease research is sorely needed to expedite answers to questions in CKD and spur better treatments and to find cures. Despite the federal government's large investment in caring people with ESRD research funding at NIH for kidney disease equaled an investment of about \$23 per person.

For the 430,000 people on dialysis² and the over 100,000 waiting for a kidney transplant³ better treatments are also needed. There are some promising products such as more portable dialysis and

¹ U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

² Ibid

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artificial kidneys in the works that could help people who are unable to get a kidney transplant live longer healthier lives. The annual mortality for those on dialysis is 21% compared to transplant which has 3.4% annual mortality.⁴ Expected survival years for transplant recipients are also much closer to that of the general Medicare population. With the scarcity of organs available for transplant it is clear greater innovation is needed in dialysis to improve patient outcomes.

We hope the 21st Century Cures initiative will help spur solutions to the barriers of innovation in the treatment of kidney disease and the National Kidney Foundation looks forward to serving as a resource on kidney disease to the committee.

Sincerely,



Kerry Willis, PhD
Senior Vice President for Health Science and Education

³ U.S. Department of Health and Human Services, Health Resources and Services Administration, Organ Procurement and Transplantation Network, accessed May 30, 2014., <http://optn.transplant.hrsa.gov/latestData/rptData.asp>.

⁴ U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.



May 30, 2014

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

Dear Chairman Upton,

On behalf of the 30 million men, women, and children affected by one of the nearly 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks Chairman Upton and the Energy and Commerce Committee for their continuing support of the rare disease community. We also thank you for commencing the 21st Century Cures Initiative, a bi-partisan effort within the House Committee on Energy and Commerce aimed at improving the treatment discovery, development, and delivery process in the United States.

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

We welcome the opportunity to comment on the 21st Century Cures Initiative's first white paper titled, "A Call to Action". This white paper raises various questions on how to improve the biomedical innovation cycle and ecosystem, including questions on incentives for drug discovery and development, unnecessary regulatory hurdles within the Federal government, and barriers to accessing treatments once on the market.

In response to these questions, NORD has developed the following legislative concepts. We are excited about the proposals below, and look forward to discussing them with the Energy and Commerce Committee as well as the entire Rare Disease Community. We also recognize that the below concepts represent only a part of the needed reforms to the treatment discovery, development, and delivery cycle for the rare disease patient. We look forward to discussing further ideas as the 21st Century Cures Initiative continues.

1. Reinstating the Orphan Products Board

To facilitate coordination more effectively among the Federal agencies with jurisdiction over the discovery, development, and delivery of orphan therapies and between these Federal agencies and the rare disease community, NORD recommends that the Committee reinstate the Orphan Products Board within the Department of Health and Human Services. The Orphan Products Board, a now dormant entity in practice but still alive in statute (42 U.S. Code § 236), was established in the Orphan Drug Act in 1983 to “promote the development of drugs and devices for rare diseases or conditions and the coordination among Federal, other public, and private agencies in carrying out their respective functions relating to the development of such articles for such diseases or conditions”.

A reinvigorated Orphan Products Board would be beneficial for the entire rare disease community. First, it would facilitate greater communication and collaboration between the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), thus strengthening the bonds between the orphan drug discovery process and the development and approval processes.

Second, a reinvigorated Orphan Products Board would facilitate greater communications between FDA and NIH and the Federal agencies that are instrumental in the delivery of orphan products, such as the Centers for Medicare and Medicaid Services (CMS) and the Department of Defense (DOD). These collaborations will assist in ensuring that critical orphan therapies will actually reach the rare disease patients who need them.

2. Establishing an Office of Clinical Trial Design within the NIH National Center for Advancing Translational Sciences (NCATS)

Clinical trial design is of a paramount importance when developing any therapy, but is especially important for orphan therapies, where innovative trial designs are often needed to accommodate the small disease population. Many companies that are developing orphan therapies are also often small, inexperienced companies that have little practice in designing clinical trials in general, let alone trials for diseases that require an innovative trial design because of factors such as small or geographically dispersed patient populations.

NORD proposes that Congress establish an Office of Clinical Trial Design within the NIH National Center for Advancing Translational Sciences. This office will house some of the foremost experts in clinical trial design, and will consult with sponsors on clinical trial design. In order to motivate sponsors to consult with this newly established office, the FDA must accept the new office’s participation in the trial design during the product development process and consider recommendations from that office when determining its approach to reviewing the application for approval of the drug.

This office would also work to ensure strong public/private partnerships in recruitment of patients for clinical trials. Working with this office, patient groups and pharmaceutical sponsors can collaborate on and participate in clinical trial design.

3. Establishing an Office of Clinical Endpoints within the NIH National Center for Advancing Translational Sciences (NCATS)

Similarly as for clinical trial design, establishing an appropriate clinical endpoint can be especially difficult for studies involving rare diseases. All clinical trials must have agreed-upon clinical endpoint(s), intermediate clinical endpoint(s) (ICE), or surrogate endpoint(s) for FDA approval.

NORD proposes the establishment of an Office of Clinical Endpoints within the NIH NCATS to address this issue. Both patient groups and biopharmaceutical companies would be able to consult with this office on clinical endpoints and biomarkers. This office would be helpful in preventing companies and/or patient organizations from spending years and millions of dollars on biomarker research only to receive a rejection from the FDA.

This office would be especially beneficial to the rare disease patient population, as clinical endpoints and biomarkers are particularly difficult to establish within rare, genetic diseases. Similar to the Office of Clinical Trial Design, it is of the utmost importance that the Office of Clinical Endpoints work closely with the FDA, and the FDA factor in this office's involvement and input when assessing potential clinical endpoints and biomarkers.

4. Training of Medical Professionals in Rare Diseases

Currently, the Federal government has various programs to incentivize medical professionals in training to enter certain specialties. NORD proposes that the Federal government establish similar incentives to study and enter fields relating to treating or researching rare diseases. There are various options Congress could take to increase the number of U.S. physicians who are knowledgeable about rare diseases. For example, Congress could implement subsidized training programs within the NIH to encourage research into rare diseases. Congress also could reform the Graduate Medical Education (GME) system to incentivize residency programs on rare diseases.

The U.S. needs more physicians and researchers educated in rare diseases. An increase in medical and scientific professionals with rare disease experience will lead to faster diagnoses, more efficient and effective care, faster discovery of cures, and overall benefits to the health system, as rare disease research will be more easily translated to more common diseases.

5. Establishing a Rare Disease Ombudsman within the Department of Health and Human Services (HHS)

Currently, the rare disease population has representation within both the FDA and the NIH, in the FDA Office of Rare Diseases and Office of Orphan Product Development, and within the NIH at the Office of Rare Disease Research. However, there is no rare disease representation within the parent Department of Health and Human Services, to ensure access to approved products. NORD proposes the establishment of a Rare Disease Ombudsman within HHS to ensure that patients with rare diseases are not subject to barriers in accessing quality coverage that meets their unique healthcare needs. The Rare Disease Ombudsman would:

1. Provide recommendations to the Secretary regarding guidelines on appeals and grievance processes and protections that ensure patients with rare disorders receive access to high quality treatment.
2. Review and advise the Secretary regarding benefit design features critical to patients with rare disorders and unmet medical needs, including, but not limited to, access to prescription drugs, out of pocket costs, and network adequacy.
3. Serve as a single point of contact for patients with rare diseases to address unique issues that impact access to care.

The HHS Rare Disease Ombudsman also would play a role in ensuring that rare disease patients are accessing the necessary care through insurance plans offered under the state marketplaces.

6. Ensuring Access to Orphan Therapies by Addressing Prohibitive Cost-Sharing Structures within both Public and Private Plans

In the 21st Century Cures Initiative's first white paper titled "A Call to Action," the Committee asks, "What uncertainties or barriers currently exist in post-market, real world delivery settings – legal, regulatory, commercial, or otherwise – and how should they be addressed?"

One of the major hurdles in ensuring patient access to orphan therapies is the increased use of high cost-sharing structures within drug plans. These prohibitive cost-sharing structures often involve upwards of 40% co-insurance on drugs placed on the highest tier within the formulary, also known as the specialty tier. These co-insurance requirements require egregious out-of-pocket costs to be paid by the patient on drugs that are extremely expensive in the first place.

There are many times when therapies are not on a plan's formulary. This often results in out-of-pocket limits no longer being applicable, thus subjecting patients to excessive out-of-pocket costs with no cap.

The Energy and Commerce Committee must address this growing trend of pharmaceutical tiering structures with a specialty tier with high co-insurance levels. Even if the Committee is able to improve the drug discovery and development process greatly, as it hopes to do under this initiative, if patients cannot access the drugs due to their prohibitive cost-sharing requirements, the patient experience will not be improved at all.

7. Reforming the Institutional Review Board (IRB) System for Assessing New Therapies

Currently, all clinical trials for new treatments, whether a drug, biologic, or medical device, must receive approval from an IRB. The systems used by IRBs are rarely transparent, and currently there is a gross oversaturation of small IRBs all using different standards, and rarely contributing to the efficacy of the drug. The current system can lengthen the drug development process.

NORD recommends that Congress study the IRB system to see if reforms would allow for treatments to reach patients faster.

8. Creating an “Orphan Protected Class” within the Medicare Part D Program

Recently, CMS proposed the removal of three protected classes from the Medicare Part D drug coverage system. After a unified outcry from the patient population, CMS withdrew the proposal.

NORD acknowledges the need for reform within the Medicare Part D Protected Class system, and would welcome a discussion with CMS with all stakeholders at the table. NORD also proposes that CMS add a Protected Class for orphan therapies. There are rarely alternatives to orphan therapies that patients with rare diseases rely on, yet these drugs are no more protected than any other drug within the Medicare Part D program.

By ensuring coverage of orphan therapies within the Medicare Part D Program, Congress will assure rare disease patients that they will receive the live-saving coverage they need under the Medicare program.

9. Establishing Clearer Federal Policies with Regard to Off-label use of Drugs

Many rare disease patients use drugs outside of FDA-approved uses, based on the judgment of their physicians that the drugs will benefit them and will not be harmful. Recently, reimbursement for off-label uses has been denied. Congress needs to address this issue aggressively, as many drugs will never be tested for the rare disease patient and, without reimbursement for appropriate off-label use as determined by the physician, these patients will be denied access to approved therapies that may change or save their lives.

At the same time, the government severely restricts what drug companies can say about new research and about off-label uses, thus cutting off information from the most knowledgeable sources. The Congress should seek new policies that permit drug companies to share appropriate information without fear of enforcement action.

Thank you again for the opportunity to engage in this exciting and much-needed initiative. We look forward to working with Chairman Upton and the Energy and Commerce Committee as the 21st Century Cures Initiative continues, and we are grateful for the Chairman's recognition of these extremely important issues within the rare disease community.

For questions regarding NORD or the above comments, please contact [REDACTED]
[REDACTED]

Sincerely,

[REDACTED]

Peter L. Saltonstall
NORD President and CEO



NATIONWIDE CHILDREN'S

When your child needs a hospital, everything matters.

The Research Institute

May 30, 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 to cures@mail.house.gov

Dear Chairman Upton and Rep. DeGette:

On behalf of The Research Institute at Nationwide Children's Hospital, thank you for launching the 21st Century Cures initiative and the opportunity to submit comments on the May 1 White Paper.

We are at a time of extraordinary opportunity in medicine and biomedical research. At our own institution, dramatic breakthroughs in our understanding of the human disease and better ways to treat childhood illness can be classified as "paradigm shifting". Similar breakthroughs are taking place around the country and an increasingly informed public is clamoring for progress at a faster pace. And while the nature of scientific progress can never be fast enough for those who are ill or injured, there are important opportunities to speed the pace of discovery.

The Research Institute at Nationwide Children's Hospital ranks among the top ten pediatric research institutions nationally, according to NIH data, and is one of the fastest growing with 13 centers of emphasis. In 2013, NIH prime awards to The Research Institute totaled \$33 million, a significant increase from \$6.9 million in 2000, and comprised half of our \$66 million research budget.

Discovery

The past decade of federal research funding stagnation is the leading challenge to discovery. The U.S. is losing its longstanding world leadership in biomedical research and development. We are slipping and we must act with speed to regain leadership. We are seeing research and development spending in Asia exceed that in the U.S. Expenditures in China are growing faster than in the U.S. as are research publications.

Those on the front lines of research are seeing an increasingly low success rate among highly qualified submissions to NIH and other federal research agencies. In the past, a researcher could know that a worthy proposal had a reasonable chance of funding success. Simply put, important research is not moving forward.

What are the major consequences of this federal funding stagnation from a talent standpoint? The loss of young talent has been widely discussed and is real. The loss of mid-career biomedical research professionals has been less widely discussed, but is also becoming real as the funding stagnation continues. And lastly, there is the two-way brain drain and for the first time it is not to

our benefit. The ability of the U.S. to draw the best and the brightest foreign scientists to our research institutions is at risk as they will increasingly be able to follow their dreams at home. And many of us know American scientists who have already moved overseas. The result is a vicious brain drain that will unwind a U.S. innovation economy that has dominated the global scene for more than a century. There is opportunity to correct this situation before our human and non-human infrastructure is too far diminished.

Pediatrics requires a particular focus. Children represent a lifetime of investment when we treat and cure them. Since their illnesses are frequently rare and therefore less attractive to commercial investment, they merit a federal investment on that basis alone. The Committee has been cognizant of the special investment challenges in pediatrics, passing both the National Pediatric Research Network Act and the Gabriella Miller Kids First Research Act within the past year. Please look for additional ways to place the spotlight on pediatrics through the 21st Century Cures initiative.

Development and Delivery

We must seek gains on the Development and Delivery continuum through increasing efficiency within FDA and coordination between FDA and NIH while maintaining or increasing safety. There is an appropriate heightened sensitivity to safety when working with children. At the same time, parents of children with a known fatal illness may be more likely to want to take risks. We have FDA and NIH experience in gene therapy and drug development which we would be happy to share. For example:

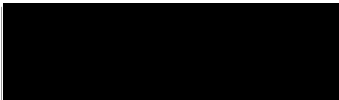
Our Center for Gene Therapy was the first to demonstrate positive results for an exon-skipping drug in a clinical trial against muscular dystrophy. The drug's manufacturer has applied to the FDA to take the next step in testing.

Here in Columbus, OH our Nationwide Children's Hospital scientists are world leaders in development of gene therapy approaches for a variety of devastating childhood diseases.

One of our leading researchers developed a vaccine for middle ear infection poised to be released throughout the industry, following over two decades of focused research.

Nationwide Children's is now home to the first FDA-approved U.S. human trial to investigate the safety and effectiveness of using tissue engineering to repair congenital heart defects.

In conclusion, thank you once again on behalf of The Research Institute at Nationwide Children's Hospital for this opportunity to comment on the first White Paper in the 21st Century Cures initiative. We hope that the Committee will work with Congress for the U.S. to remain a leader in Discovery with a special emphasis on pediatrics, and we offer our expertise in examining approaches to streamlining the development and delivery process.



Ann I. Wolfe Endowed Chair in Pediatric Research
President, The Research Institute at Nationwide Children's Hospital
Professor and Vice-Chair, Department of Pediatrics
The Ohio State University College of Medicine



May 30, 2014

The Honorable Fred Upton
Chairman
Committee on Energy & Commerce
2215 Rayburn House Office Building
Washington, DC 20515

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

Dear Chairman Upton and Ranking Member DeGette:

Nemours thanks you for your leadership in establishing the 21st Century Cures Initiative. Nemours is an internationally recognized children's health system that owns and operates the Nemours/Alfred I. duPont Hospital for Children in Wilmington, Del., and Nemours Children's Hospital in Orlando, along with major pediatric specialty clinics in Delaware, Florida, Pennsylvania and New Jersey. Established as The Nemours Foundation through the legacy and philanthropy of Alfred I. duPont, Nemours offers pediatric clinical care, research, education, advocacy and prevention programs to families in the communities it serves. As you consider policy opportunities to close the gap between the number of diseases and the number of treatments, **Nemours urges you to incorporate a focus on pediatric research. We recommend that the Committee convenes a roundtable, hearing and comment request specific to the needs of the pediatric population, as well as inclusion of provisions to accelerate the advancement of pediatric cures in any final legislative package or other vehicle that the Committee advances.**

The comments below address the following questions posed by the Committee.

Key Questions from the Committee

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

Funding

"Research into the causes, preventions, and treatments of diseases that begin very early in life will have a profound, lifelong impact on disease burden and financial costs."ⁱ Yet, a lack of adequate research resources is a major challenge in accelerating cures for pediatric diseases.

Even during the period of NIH doubling, the proportion of the NIH budget devoted to pediatric research declined overall.ⁱⁱ This underfunding affects treatments for pediatric cancer, as well as rare diseases. Whereas the biopharmaceutical sector funds approximately 60 percent of all biomedical research in the U.S., the private sector has made an "almost negligible investment" in childhood cancerⁱⁱⁱ even though cancer is the leading cause of death by disease among children under age 15 in the U.S.^{iv} This puts a greater onus on the NIH, specifically the National Cancer Institute (NCI), as well as the philanthropic sector, to fund pediatric cancer research. Yet only 3.8 percent of all cancer research funding allotted by the federal government goes to children.^v Moreover, the Children's Oncology group (COG), which is a

pediatric cooperative group devoted exclusively to childhood and adolescent cancer research, has experienced a 30 percent decrease in base funding since 2004 from NCI, adjusting for inflation.^{vi}

Pediatric rare diseases also merit greater attention and funding. Unfortunately, “very few studies have addressed the needs of the pediatric population with rare diseases separately from that of adults. However, since nearly 50 to 75 percent of rare diseases begin in childhood, these pediatric diseases deserve special priority.”^{vii}

Nemours recommends that Congress appropriate additional funding for NIH that ensures a steady, predictable source of grant funding for the pediatric population to help accelerate research for pediatric diseases and conditions, including rare diseases.

National Pediatric Research Network Act Implementation

The National Pediatric Research Network Act (NPRNA), signed into law as part of the PREEMIE Reauthorization Act, authorizes the NIH to create a national network of research consortia to accelerate discoveries in pediatrics by incenting increased collaboration, coordination and sharing of core research infrastructure across multiple institutions. In pediatrics, where most of our conditions are rare diseases, there is a need for multi-institution initiatives, which the network would help to spur. Many rare diseases are “highly complex, childhood-onset, multi-system disorders that are often associated with developmental disability, and require lifelong, highly specialized care and support.”^{viii} Unfortunately, there is currently no cure for many rare diseases, but advances in research can help to improve quality of life and work towards a cure.

To coordinate and accelerate research for diseases or conditions we know relatively little about, Nemours recommends that Congress work with the NIH to fully implement the NPRNA.

Pediatric Drug Studies and Clinical Trials

The Pediatric Research Equity Act (PREA) requires drug companies to study their products in children under certain circumstances. However, when pediatric studies are required, they must be conducted with the same drug and for the same use for which they were approved in adults.^{ix} This means that if a drug company develops a drug to treat lung cancer in the adult population, the company would not be required to do a study in the pediatric population, despite the fact that the molecular target of new cancer drugs might be important for childhood cancers.^x

As part of a hearing, roundtable or comment request, Nemours urges the Committee to solicit feedback as to whether this provision should be revisited to require that appropriate studies be performed on the pediatric population, based on the relevance of the drug’s target to childhood cancer, regardless of the organ, origin or type of cancer.^{xi}

Drug testing is only one piece of the puzzle, though. Continuing to test adult drugs in children does not go far enough; instead, we need the NIH and Food and Drug Administration (FDA) to incentivize or require *pediatric drug development*. “The types of cancers that develop in children are often different from the types that develop in adults.”^{xii} Whereas adult cancers often occur in exposed tissues such as the skin, lungs, prostate, breast or colon, children get cancer in protected tissues like bone, muscle, nerves, brain and bone marrow. The different causes of these cancers require different treatments.

Toward that end, Nemours urges the Committee to solicit feedback as to how to best incentivize or require that a certain percentage of a drug company's portfolio has pediatric indications.

Clinical trials are prohibitively expensive, and this is particularly the case when conducting trials with children, as compared to studies in adults. The expense of pediatric trials stymies the conduct of important trials of drugs that have been approved in adults. Additional innovative designs for clinical trials in pediatric patients need to be developed, with input from FDA, to become part of the approval process. Capitalizing on technologies such as remote data entry and video virtual visits that allow children to participate in research at offsite locations will likely improve recruitment and retention, allow for a greater diversity of children to participate, and is particularly applicable to children with rare diseases who are scattered geographically at long distances from medical research centers. These technologies should be further refined and developed for research purposes and incorporated into pediatric clinical trials.

Nemours urges the Committee, as part of a hearing or roundtable, to solicit feedback regarding how to accelerate the development and implementation of innovative designs for clinical trials in *pediatric* patients, with a goal of facilitating greater participation in trials, at a lower cost.

Thank you again for your leadership and commitment to advancing research to develop cures. Nemours looks forward to working with you to address issues affecting the pediatric community. Please feel free to reach out to [REDACTED] for additional information.

Sincerely,

[REDACTED]

Vicky L. Funanage, Ph.D.
Director, Biomedical Research
Nemours

ⁱ William W. Hay, Jr., MD, Daniel P. Gitterman, PhD, David A. Williams, MD, George J. Dover, MD, Theodore C. Sectish, MD, and Mark R. Schleiss, MD. *Pediatrics*. June 2010, 125(6):10.1542/peds.2009-2635.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857014/>

ⁱⁱ William W. Hay, Jr., MD, Daniel P. Gitterman, PhD, David A. Williams, MD, George J. Dover, MD, Theodore C. Sectish, MD, and Mark R. Schleiss, MD. *Pediatrics*. June 2010, 125(6):10.1542/peds.2009-2635.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857014/>

ⁱⁱⁱ Guest Editorial of Peter C. Adamson, MD, Chair, Children's Oncology Group.
http://www.cancerletter.com/articles/20140523_4_May_23_2014.

^{iv} Pediatric Cancer Foundation. Retrieved from: <http://fastercure.org/about-us/facts-about-childhood-cancer/>

^v Pediatric Cancer Foundation. Retrieved from: <http://fastercure.org/about-us/facts-about-childhood-cancer/>

^{vi} Guest Editorial of Peter C. Adamson, MD, Chair, Children's Oncology Group.
http://www.cancerletter.com/articles/20140523_4_May_23_2014.

^{vii} Supriya Bavisetty, Wayne W. Grody and Shahram Yazdani. *Emergence of pediatric rare diseases. Review of present policies and opportunities for improvement*. Landes Bioscience, 2013.

<https://www.landesbioscience.com/journals/rarediseases/2012RAREDIS000.pdf>

^{viii} <http://www.ncbi.nlm.nih.gov/pubmed/23696535>

^{ix} <http://blogs.fda.gov/fdavoices/index.php/tag/pediatric-research-equity-act-prea/>

^x Testimony of Peter c. Adamson, MD, Chair, Children’s Oncology Group before the 2nd Annual Childhood Cancer Summit, hosted by the House Childhood Cancer Caucus, September 23, 2011. <http://childhoodcancer-mccaul.house.gov/issue/bpca-and-prea-reauthorization>

^{xi} Testimony of Peter c. Adamson, MD, Chair, Children’s Oncology Group before the 2nd Annual Childhood Cancer Summit, hosted by the House Childhood Cancer Caucus, September 23, 2011. <http://childhoodcancer-mccaul.house.gov/issue/bpca-and-prea-reauthorization>

^{xii} American Cancer Society. “What are the differences between cancers in adults and children?”

<http://www.cancer.org/cancer/cancerinchildren/detailedguide/cancer-in-children-differences-adults-children>



Daniel Casserly
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May 30, 2014

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

Dear Chairman Upton and Congresswoman DeGette:

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. We apply our expertise in science and innovation to meet society's biggest health challenges by focusing on patients' needs and following the science. Novartis offers a diversified portfolio of products including innovative medicines, eye care, preventive vaccines, over-the-counter and animal health products. Novartis has discovered innovative treatments for disorders ranging from cancer to degenerative diseases.

We have supported previous efforts to improve drug development. Most recently, we were involved with the development of the Food and Drug Administration Safety and Innovation Act (FDASIA), and have supported FDA's efforts to implement this important law. FDASIA included needed improvements to FDA's expedited pathways, specifically breakthrough therapy designation (BTD). The breakthrough designation was included in FDASIA to increase collaboration between FDA and sponsors during the drug development process when preliminary clinical evidence demonstrates that a drug may offer substantial improvements over available therapies.

Novartis is a proponent and early adopter of the breakthrough designation. To date, four of our products have received breakthrough designations - one of which, ceritinib (Zykadia), was recently approved for the treatment of patients with advanced non-small cell lung cancer. We believe these types of improvements to the drug development and application review processes can help ensure that innovative medicines reach patients in a more efficient manner. Additionally, we believe FDASIA placed an important emphasis on the need for improvements in the areas of regulatory science, specifically rare disease drug development and patient-focused drug development (PFDD). We believe these are key areas that require additional consideration from efforts like 21st Century Cures.

Innovation in research and development is a key focus of Novartis. In this vein, we are supportive of the 21st Century Cures: A Call to Action which necessarily highlights the need for additional attention to the discovery, development, and delivery of new treatments and cures. We note that in the last decade or so, several initiatives have been proposed that have sought to enhance the "discovery, development and delivery" of medicines, including the Critical Path Initiative, Advancing Regulatory Sciences, and President's Council of Advisors on Science and Technology (PCAST). The 21st Century Cures initiative could provide needed coordination, oversight and funding for these efforts.

As ardent supporters of integrating new, innovative methods and ideas into the drug development paradigm, Novartis would like to participate in the House Energy and Commerce Committee's 21st Century Cures bipartisan initiative. We believe this initiative could provide significant benefits to ongoing but perhaps languishing initiatives or new efforts to ensure that patients obtain access to safe and effective medicines in an efficient manner.

Sincerely,

Dan Cassery

June 1, 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 engaging the community on the 21st Century Cures initiative. Your focus on accelerating the pace of medical breakthroughs should generate ideas and legislation that greatly improve the quality of patient care in the United States, including proposals to promote personalized medicine, which is on the cutting edge of biomedical innovation.

This letter is in response to your request for comments published in the white paper entitled *21st Century Cures: A Call to Action*.

The Personalized Medicine Coalition (PMC) is an education and advocacy organization that promotes the understanding and adoption of personalized medicine to benefit patients and the health care system. We represent more than 225 academic, patient, provider, and payer organizations, as well as drug and diagnostic manufacturers and clinical laboratories. Given the hopes and desires of this diverse group of stakeholders united in PMC, the Coalition has a keen interest in the 21st Century Cures initiative.

Personalized medicine uses diagnostic tools to identify specific biological markers, often genetic, that can help assess which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical history and circumstances, personalized medicine allows doctors and patients to develop cost-saving, targeted prevention and treatment plans. Personalized medicine, therefore, has the potential to optimize the delivery and dosing of treatments so patients can receive the most benefit at the least amount of risk and harm, eliminating both the unnecessary side effects of toxic treatments such as chemotherapy and the delays associated with the "trial-and-error" process that many patients endure to obtain the correct diagnosis and treatment for their condition.

At a time of unprecedented scientific and medical breakthroughs, personalized medicine has the capacity to more accurately diagnose human diseases, predict individual susceptibility to disease, detect the onset of disease at early stages, pre-empt its progression, target treatments, and increase the overall efficiency and effectiveness of the health care system.

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These advances have already impacted the way we treat patients. Metastatic melanoma and certain types of lung cancer are now further classified by their molecular signatures, and are treated with the drug that is most likely to improve the patient's chance of survival based on that signature. The number of personalized medicine products has more than quadrupled in recent years, from only 13 on the market in 2006 to more than 70 in 2012. These innovations are changing the face of health care today, as researchers further investigate the heterogeneity of disease and work together to develop solutions that improve patient care and reduce overall health care costs.

But our current system is not capable of managing the new characterization of diseases. Many of our most costly and prevalent diseases are in fact a collection of different diseases. Soon we will be able to correctly categorize them as distinct entities, thereby aiding treatment, and ideally, contributing to the development of cures for diseases such as type-2 diabetes, schizophrenia, and cystic fibrosis. The change in how we characterize disease will require resources to retrain health care professionals, adopt new infrastructure, and identify new ways to inform patients so that they can better understand their condition.

Current progress in personalized medicine is a harbinger of much greater things to come. Patients with rare and devastating diseases can now lead normal and economically productive lives, and in doing so decrease the overall health care burden and dramatically increase their own quality of life. Previously devastating cancers can now be treated while patients remain productively employed, and children with certain genetic conditions can be diagnosed and treated early, enabling them to lead normal lives.

The concept of personalized medicine, however, presents challenges to health care policymakers. At the heart of these challenges is the fact that while conventional policy has treated therapeutic agents, diagnostic tests, and health care services as separate policy issues, personalized medicine requires that policies governing these different segments of health care be aligned.

POLICY SUGGESTIONS

As outlined in the white paper, many have recognized that to reap the rewards of our \$3 billion federal investment in mapping the human genome, comprehensive policy adjustments must be made. PMC has identified a number of concepts that would enhance patient health care delivery through personalized medicine.

PMC's advocacy activities focus on regulatory policy, reimbursement and payment policies, and incentives for biomedical innovation. In this letter, we briefly outline our suggestions in the areas where we think Congressional intervention could have maximum impact.

Regulatory Policy:

Incentivize personalized medicine by creating a transparent, stable, and predictable regulatory environment for personalized medicine products that is flexible enough to respond to the emerging science.

This can be accomplished through coordinated review of personalized medicine products and concurrent review of qualified, co-developed analyte diagnostics, as augmentation to the current expedited review pathway for breakthrough therapies. Under current law, the timing of the FDA's review of a drug/biologic is unrelated to the timing of the agency's review of the test designed to guide its use.

Reimbursement and Payment Policies:

Assure that coverage and reimbursement policies support continued innovation and adoption of personalized medicine.

Federal payment policies should incentivize personalized medicine and accommodate personalized approaches to care, as opposed to basing decisions on average responses. CMS is currently exploring alternative models for

paying for health care. CMS could be charged with designing new models that support personalized medicine. For example, under current law, whether Medicare provides coverage for a particular drug/biologic is independent of whether it provides coverage for a particular diagnostic, and vice versa. Medicare statute should be altered to provide coverage of a personalized medicine diagnostic test that is prescribed, recommended, referenced, or suggested for use in the FDA-approved labeling of a personalized medicine drug/biologic for which Medicare coverage is available.

Incentives for Biomedical Innovation:

Encourage research by the public and private sectors as well as public-private partnerships.

This could be accomplished by supporting the National Institutes of Health (NIH) and the research and development credits that encourage innovation. The NIH has fueled the American biomedical innovation engine by educating young scientists and encouraging the science that supports quality improvements in health care. The availability of the Qualifying Therapeutic Discovery Tax Project tax credit/cash grant program, designed to encourage projects aimed at treatments for unmet medical needs and/or prevent, detect, or treat chronic or acute diseases and conditions, should be extended. Furthermore, the risks of co-developing therapeutic-diagnostic combinations could be reduced through the establishment of a new research and development tax credit that encourages the development of novel personalized medicines and their co-developed diagnostics.

We hope you will find the following educational materials useful to the 21st Century Cures initiative.

EDUCATIONAL MATERIALS

The Case for Personalized Medicine

Outlines the current state of personalized medicine science, policy, and business. It is the go-to resource on this topic. It includes a table of personalized medicine products, real-world examples that demonstrate how personalized medicine is improving the quality of patient care, and a discussion of policies impacting the field.
[http://www.personalizedmedicinecoalition.org/Resources/The Case for Personalized Medicine](http://www.personalizedmedicinecoalition.org/Resources/The_Case_for_Personalized_Medicine)

Pathways for Oversight of Diagnostics

Outlines the laws and regulations that govern personalized medicine diagnostics so that all stakeholders can share a common understanding of the current system as they seek to define improvements to it.
[http://www.personalizedmedicinecoalition.org/Resources/Pathways for Oversight of Diagnostics](http://www.personalizedmedicinecoalition.org/Resources/Pathways_for_Oversight_of_Diagnostics)

Personalized Medicine by the Numbers

Quantifies progress in the field.

[http://www.personalizedmedicinecoalition.org/Resources/Personalized Medicine by the Numbers](http://www.personalizedmedicinecoalition.org/Resources/Personalized_Medicine_by_the_Numbers)

The Future of Coverage and Payment for Personalized Medicine Diagnostics

Defines the personalized medicine reimbursement landscape so that all stakeholders can share a common understanding of the current system as they seek to define improvements to it.

[http://www.personalizedmedicinecoalition.org/Resources/The Future of Coverage and Payment for Personalized Medicine Diagnostics](http://www.personalizedmedicinecoalition.org/Resources/The_Future_of_Coverage_and_Payment_for_Personalized_Medicine_Diagnostics)

CONCLUSION

PMC commends the House Energy and Commerce Committee's work and shares in your goal of charting the course for discovery, development, and delivery of health care advancement by promoting new policies that support innovation and the development of products and services that deliver high-quality, efficient, patient-centered care. We will expand on our policy suggestions in the coming months.

PMC appreciates the opportunity to provide comments on the 21st Century Cures initiative. If you have any questions about these comments or would like more details, please contact me at [REDACTED]

Sincerely,

[REDACTED]

Amy M. Miller, Ph.D.
Executive Vice President
Personalized Medicine Coalition (PMC)



Pulmonary Hypertension Association

Empowered by hope

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May 28, 2014

The Honorable Fred Upton
2183 Rayburn House Office Building
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Washington, DC 20515

The Honorable Diana DeGette
2368 Rayburn House Office
Washington, DC 20515

Dear Chairman Upton and Ranking Member DeGette:

Thank you for providing the opportunity to comment on the Energy and Commerce Committee's white paper, "21st Century Cures: A Call to Action." During my sixteen years as the President of the Pulmonary Hypertension Association (PHA), pulmonary hypertension (PH) has gone from having one available treatment to having twelve. That is more treatments than all but two of the 7,000 rare diseases in the U.S. Unfortunately, I have also seen many examples of the ways this country's declining investment in biomedical research and related programs is undermining our international competitiveness. I am pleased that the Energy and Commerce Committee is committed to finding ways to maintain, and even strengthen, U.S. investment in the treatment pipeline.

ABOUT PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a disabling and often fatal condition simply described as high blood pressure in the lungs. It affects people of all ages, races and ethnic backgrounds. Although anyone can get PH, there are risk factors that make some people more susceptible.

Treatment and prognosis vary depending on the type of PH. In one type, pulmonary arterial hypertension (PAH), the arteries in the lungs become too narrow to handle the amount of blood that must be pumped through the lungs. This causes several things to happen: a backup of blood in the veins returning blood to the heart; an increase in the pressure that the right side of the heart has to pump against to push blood through the lungs; and a strain on the right side of the heart due to the increased work that it has to do. If this increased pressure is not treated, the right side of the heart can become overworked, become very weak and may fail. Because the blood has difficulty getting through the lungs to pick up oxygen, blood oxygen level may be lower than normal. This not only strains the heart, but also decrease the amount of oxygen getting to the brain.

There is currently no cure for PAH. Twelve treatment options are available to help patients manage their disease and feel better day to day but even with treatment, life expectancy with PAH is limited.

ABOUT THE ASSOCIATION

From simple beginnings – four women who met around a kitchen table in

Florida in 1990 – the Pulmonary Hypertension Association has evolved into a community of well over 10,000 pulmonary hypertension patients, caregivers, family members and medical professionals.

As we have grown, we have stayed true to our roots and the vision and ingenuity of our founders: *We continue to work every day to end the isolation that PH patients face, and find a cure for pulmonary hypertension.*

BIOMEDICAL RESEARCH AND PH

PHA recently asked members of the clinical and scientific community specializing in PH which areas of progress could be attributed to research supported by the National Institutes of Health. PHA's medical and scientific leadership stated **“All of them! There has been no progress made in the understanding, diagnosis and treatment of pulmonary hypertension that cannot be traced back to the work of the National Institutes of Health.”**

The Pulmonary Hypertension Association is pleased to partner with the National Institutes of Health to award a KO8/K23 grant each year. We are proud to report that the all awardees have been retained in research, both basic and clinical, and have published more than 200 scientific articles catalogued in PubMed at the National Library of Medicine. In addition, awardees have generated substantial additional funding from the NIH and other granting agencies to further promote their research.

The rapid progression in understanding and treating pulmonary hypertension is the result of decades of federally-funded research. That investment must continue if we are to continue to maintain our momentum and capitalize on the opportunities for novel, life-saving therapies that would be unlikely to be explored by private industry.

PHA also appreciates our partnerships with AHRQ, PCORI, HRSA, FDA, CDC and other federal agencies on initiatives that improve health outcomes for those living with pulmonary hypertension.

TWO RESEARCHERS' STORIES

On April 26, as a member of the American Thoracic Society's Research Advocacy Committee, I participated in visits to Members of Congress. A key talking point for our visits was asking Congress to support NIH funding. As we made our visits, I was struck by the story a researcher in our group told in each office we visited:

“Look at me. I am your success story. I received an NIH research grant and I advertised for my staff. Every one of the applications I received was from China and India. They will come and learn and take my knowledge back to their country and it will be lost to us.

Why?

Because U.S. doctors know that with a roughly one in ten likelihood of a grant – down from one in three a few years ago – they have little chance at a first grant...and next to no chance to get a second grant that will assure their careers in research. They are building their careers elsewhere.”

Here is a related story.

Coming back from a trip to Taiwan several years ago, I had a conversation with the passenger seated next to me. He asked me where I lived and when I told him suburban Maryland, he said, “I used to live in Bethesda.” I asked him what he did and he said, “I'm a researcher in Oncology. I used to work at NIH.” When I asked why he left, he responded, “Research money has dried up in the U.S. It's flowing in Asia.”

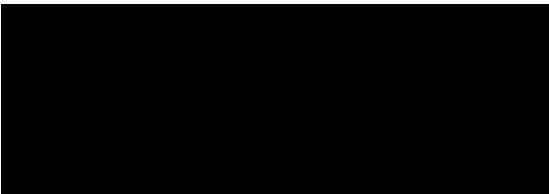
AREAS FOR INVESTMENT

PHA applauds “21st Century Cures: A Call to Action” for its recognition this country cannot solve our drug-development challenges with the same thinking we have used for the past decade; that continued investment in NIH, FDA, CDC, HRSA, PCORI, AHRQ and related agencies are critical to our economic well-being; and that new, more flexible models are needed for clinical trials and drug approval. Those models must take into consideration the needs of pediatric patients. About half of the 7,000 rare diseases in the U.S. affect children and PH is one of them. While there are twelve treatments available for adults with PH, none are approved for children.

On May 13, FDA hosted a meeting with the pulmonary arterial hypertension community. They asked PAH patients important questions about life with the disease and the pros and cons of available treatments. In the meeting we heard two things loud and clear: that each PH drug works differently for each patient and that none of them allow patients to return to the same level of activity they enjoyed before becoming sick. There are still important questions to resolve, including the level of risk that PAH patients find acceptable in clinical trials, but we believe that FDA’s Patient Focused Drug Development Initiative provides an important model for engaging patients in multiple steps of the drug-development process. We are grateful for the opportunity to participate in the program and look forward to the expansion of it and other unique approaches to addressing our nation’s drug-development challenges.

In conclusion, the best ways to advance innovation in the U.S. treatment pipeline is by making sure that all federal research programs have robust funding in FY15 and moving forward.

Sincerely,



Rino Aldrighetti
President



May 30, 2014

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

The Honorable Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Re: *21st Century Cures: A Call to Action White Paper*

Dear Chairman Upton and Congresswoman DeGette:

The Alliance for Home Dialysis (Alliance) appreciates the opportunity to provide the Energy and Commerce Committee with comments on the 21st Century Cures initiative and the *21st Century Cures: A Call to Action* white paper. The Alliance shares the Committee's goal to "accelerate the discovery, development, and delivery of promising new treatments to patients" and looks forward to working with the Committee throughout its process to help to identify policies to accomplish this goal for home dialysis patients.

The Alliance is a coalition of kidney dialysis stakeholders, representing patients, clinicians, providers and industry. We have come together to promote activities and policies to facilitate treatment choice in dialysis care while addressing systemic barriers that limit access for patients and their families to the many benefits of home dialysis.

As you may know, today more than 600,000 Americans are living with end-stage renal disease (ESRD), a ten-fold increase compared to 1980.¹ This number will likely continue to increase, as an estimated 26 million people in the United States have chronic kidney disease and are at risk for kidney failure. Due to the limited number of kidneys available for transplantation, the vast

¹ U.S. Renal Data System. 2013 USRDS Annual data Report: Volume 2, "Atlas of End-Stage Renal Disease in the United States." Washington, D.C.: National Institute of Diabetes and Digestive and Kidney Diseases, May 2014. Web.

majority of ESRD patients, approximately 70 percent, depend on dialysis to replace kidney function.²

Home dialysis—peritoneal dialysis (PD) and home hemodialysis (HHD)—is an important treatment option that offers patients significant quality of life advantages, including clinically meaningful improvements in physical and mental health. For instance, because HHD offers more frequent and/or lasting dialysis sessions, studies demonstrate individuals have a quicker recovery time after treatment³ and have an increased opportunity for rehabilitation.⁴ PD patients experience fewer negative side effects, such as nausea, and dietary restrictions than in-center patients.⁵ However, today, only 10% of U.S. dialysis patients receive treatment at home, with less than 2% of patients receiving HHD.⁶

Congress' stated intent in the creation of the End Stage Renal Disease (ESRD) benefit was that "the maximum practicable number of patients who are medically, socially, and psychologically suitable candidates for home dialysis or transplantation should be so treated."⁷ The Alliance believes that the work the Committee is embarking on to align policies with technological advances in order to ensure patients have access to new treatments, new applications and new products in a timely manner could help the kidney community to fully realize this goal. While research is underway to look at ways to prevent ESRD and improve treatments (including creating an artificial kidney), greater investment in these concepts is needed to bring them to light faster.

Many innovations are a long way off from benefitting those who have or who are moving towards kidney failure today. One way to have a more immediate improvement in options for treating kidney failure is to focus on improving upon existing options for home dialysis. We have a shared interest in improving patient outcomes and experiences, and the Alliance believes that the discovery, development and delivery of new interventions for dialysis patients is critical and should include innovations in home dialysis, which can provide meaningful clinical and quality of life benefits to those living with ESRD.

One way to achieve this goal is to include the patient perspective in the development of new technologies. The Food and Drug Administration (FDA) has started this process with a workshop

² The Medicare Payment Advisory Commission. Report to the Congress: Medicare Payment Policy, Chapter 6, "Outpatient Dialysis Services". Washington, DC: MedPAC, March, 2014. Web. http://www.medpac.gov/documents/Mar12_EntireReport.pdf

³ Heidenheim AP, Muirhead N, Moist L, et al. Patient Quality of Life on Quotidian Hemodialysis. *Am J Kidney Dis*. 2003 Jul; 42(1 Suppl):36-41.

⁴ Blagg, Christopher. "It's Time to Look at Home Hemodialysis in a New Light." *Hemodialysis Horizons: Patient Safety & Approaches to Reducing Errors*. (2006): 22-28. Web. 12 Apr 2012. <http://www.aami.org/publications/HH/Home.Blagg.pdf>.

⁵ "A Brief Overview of Peritoneal Dialysis." DaVita, Inc., Web. 16 Jul 2012. <http://www.davita.com/treatment-options/home-peritoneal-dialysis/what-is-peritoneal-disease-a-brief-overview-of-peritoneal-dialysis/t/5483>.

⁶ U S Renal Data System, *USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012.

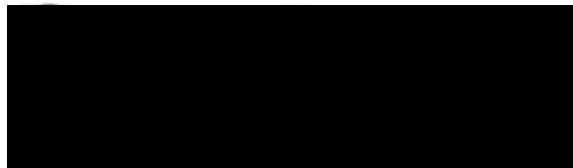
⁷ Section 1881(c)(6) of the Social Security Act.

held in September of last year titled, *The Patient Preference Initiative: Incorporating Patient Preference Information into the Medical Device Regulatory Processes*.⁸ The Alliance attended and provided input at the event. We strongly support FDA's efforts to incorporate the patient perspective in the approval process and encourage the Committee to prioritize this type of engagement when considering ways to accelerate treatments and cures to patients.

The FDA, though, has not yet articulated its next steps to realize the full potential of this effort or the timing for such activities. We recommend that the Committee reach out to the FDA to solicit next steps and request an action plan on how they plan to incorporate patient preference into the medical device regulatory process on existing and future device approval applications. We are also aware that the broader kidney community is involved in ongoing discussions with the FDA on this topic through the Kidney Health Initiative (KHI). We encourage the Committee to consider this FDA-KHI initiative ("Workshop to Elucidate Role of Patient Preferences in Support of CDRH Regulatory Actions in Kidney Disease") and ways to support its activity, as well as similar efforts to incorporate the patient perspective in FDA processes as part of the Committee's work on 21st Century Cures. The home dialysis patient community is eager to offer its perspective and to be a constructive part of the FDA approval process.

The Alliance applauds the Committee for its work on this initiative and the inclusive nature of its approach to understanding how to accelerate cures for Americans living with serious chronic illnesses like ESRD. We look forward to being an active participant in this ongoing discussion. Thank you for the opportunity to provide these comments.

Sincerely,

A large black rectangular redaction box covering the signature of Stephanie Silverman.

Stephanie Silverman
Executive Director

⁸ <http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm361864.htm>



Signing Alliance Members

American Association of Kidney Patients

American Kidney Fund

American Nephrology Nurses Association

American Society of Nephrology

American Society of Pediatric Nephrology

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Renal Physicians Association

Renal Support Network

Satellite Healthcare

Southwest Kidney Institute

TNT Moborg International Ltd.



Statement Submitted by:

Ryan Sysko, CEO
WellDoc, Inc.

To the U.S. House of Representatives
Energy and Commerce Committee

Regarding the
21st Century Cures Initiative

May 30, 2014

Dear Chairman Upton, Ranking Member Waxman and Members of the Committee:

Thank you for this opportunity to share WellDoc's experience with utilizing technology to develop new therapies for patients across the country and around the world. We commend the Committee for establishing the 21st Century Cures Initiative, and by doing so, creating a forum to discuss what is needed across industry, academia and government to ensure that the United States remains in the forefront in biomedical innovation.

WellDoc is one of the leading providers of mobile health ("mHealth") solutions in the world. Our mission is to improve the lives of people with chronic diseases. We fulfill our mission by integrating best-in-class clinical, behavioral, and motivational algorithms into software applications that can be accessed by patients and healthcare providers through highly scalable and everyday technologies, like cell phones and the web. WellDoc's solutions successfully engage patients and healthcare providers in ways that dramatically improve outcomes and significantly reduce healthcare costs.

Improved Patient Outcomes:

Achieving significant clinical outcomes through the use of technology requires that solutions transcend simple patient data collection and sharing – it is not enough. Effective solutions must transform raw patient data into valuable information and actionable knowledge to empower patient and healthcare provider decision making. WellDoc's flagship product, BlueStar® (www.bluestardiabetes.com), accomplishes this; it utilizes a simple patient interface to capture diabetes related data and then analyzes that data using proprietary and advanced analytics. Patients receive real-time coaching and support in the self-management of their disease. WellDoc also analyzes the data longitudinally to identify relevant trends and patterns to support the optimization of the patients' treatment over time. The trends and patterns are shared with patients' healthcare providers along with recommendations on how to best manage the patients' care plans.

FDA Clearance:

BlueStar is regulated as a class II medical device cleared through the 510k process. The FDA considers BlueStar to be a device even though WellDoc does not currently supply any hardware with its software – patients can use BlueStar with their existing web-enabled cell phones and computers. BlueStar's clearance by the FDA enables WellDoc to offer adults with type 2 diabetes real-time coaching and their healthcare providers with clinical decision support to assist in the management of their patients' diabetes. WellDoc's staff worked closely with the FDA as agency staff navigated the un-chartered waters of mobile medical devices. To this end, we concur with the following statement made in the 2013 report of the President's Council of Advisors on Science and Technology (PCAST) that states:

“To develop such guidances in a timely manner while reflecting high level expertise, the FDA may need to more heavily rely upon the biomedical community to collaboratively suggest standards and pathways that the agency can then consider in developing guidance documents to clarify its policies and practices.”

Further, we support Recommendation #7 in the PCAST report that calls for Reform Management Practices at the FDA, including “establishing a Commissioner’s Advisory Board for Medical Products to improve management and ensure consistent implementation of reforms.”

Cost-Savings:

Our BlueStar® Diabetes Mobile Prescription Therapy has demonstrated substantial cost savings for those healthcare providers utilizing this solution. A one-year study published in the 2011 *Journal of Health Communications* reported hospitalizations reduced by 100% and ER visits reduced by 50%! Further, 100% of patients found the product helpful and said it increased their glucose testing. An additional six-month study found a 55% reduction in hospital admits and a 16% reduction in ER visits. The cost savings are significant enough to capture the attention of any health plan administrator, and are an additional benefit after improved patient outcomes.

Reimbursement:

Unfortunately, the improved patient outcomes and substantial cost savings achieved by BlueStar® are limited to the health plans that have made the decision to utilize this solution. There are millions of type 2 diabetes patients in the United States who are on Medicare and do not have access to this real-time coaching that can assist with their diabetes management. Further, the Federal government is not benefitting from the substantial cost savings achieved by reduced hospital admits and ER visits for patients utilizing this technology. We urge the Committee to work with others in Congress to ensure that innovative biomedical therapies can be quickly approved for reimbursement by Medicare and Medicaid so that all can benefit from technological breakthroughs, while Federal taxpayers can benefit from the cost savings achieved by new solutions.

Conclusion:

Biomedical technology is a new and growing field. In nine short years, WellDoc has progressed from a start-up concept to a company with roughly 100 employees and offices in two states. However, WellDoc’s greatest impact is not in developing innovative solutions or creating jobs -- but rather its helping the millions of patients in need of better tools to manage their chronic diseases.

On behalf of all of my colleagues at WellDoc, we thank all of the Members of the Energy & Commerce Committee for seeking to identify which policies and regulations will best foster the cycle of discovery and development to keep biomedical innovation thriving in the United States. Please be in touch if you have any questions or comments about WellDoc or our products.



June 1, 2014

The Honorable Fred Upton
Chairman
House Energy and Commerce Committee
2125 Rayburn House Office Building
United States House of Representatives
Washington, DC 20515

The Honorable Diana DeGette
Member
House Energy and Commerce Committee
2125 Rayburn House Office Building
United States House of Representatives
Washington, DC 20515

Via Electronic Mail to: Cures@house.mail.gov

Re: Request for Information (RFI) Regarding the May 1, 2014 Energy and Commerce Committee
White Paper, *21st Century Cures: A Call to Action*

Dear Chairman Upton and Representative DeGette:

The American Clinical Laboratory Association (ACLA) applauds the Energy and Commerce Committee for undertaking the 21st Century Cures initiative. ACLA shares the Committee's goal of facilitating and accelerating the pace of biomedical innovation to ensure the United States remains a world leader in health care and patients have access to more effective and higher quality care. Laboratory diagnostics are an essential component to providing the most effective and highest quality care and ACLA is eager to participate in the 21st Century Cures discussion.

ACLA is a not-for-profit association representing the nation's leading providers of clinical laboratory services, including national, regional and esoteric laboratories, as well as academic medical centers throughout the United States. ACLA member laboratories are centers of diagnostic innovation, and conduct billions of laboratory tests each year which empower patients and their physicians to diagnose and treat countless diseases and medical conditions.

From a clinical standpoint, clinical laboratory diagnostic services furnish patient-specific clinical information that guides more than 70% of all medical decisions made by health care providers. Clinical laboratory tests provide objective information on the functioning of the human body, so that patients can be diagnosed, treated, or monitored accurately, precisely and as quickly as possible. The information provided by these tests, which are performed on samples of a patient's tissues or fluids, provide the necessary data for physicians to make informed decisions and best direct patient care.

Over the last few decades, laboratory medicine has seen many exciting advances in the areas of cancer, infectious disease, rare disease, and numerous other health conditions, which are helping us to realize the goal of personalized medicine. These advances have fundamentally changed our understanding of the mechanisms of disease, enabling physicians to diagnose conditions more precisely, detect the onset of disease earlier, target patient treatments more effectively, monitor disease progression, and predict individual predisposition to disease due to genetic or molecular factors. Simply put, clinical laboratory services are providing more accurate diagnoses, quicker; allowing physicians and patients to choose the best treatment, first and sooner; and, in the process, increasing the quality of life, lowering costs, and saving lives.

America's clinical laboratories are complex health care operations staffed by highly skilled and specialized pathologists, geneticists, laboratorians and technicians operating in highly controlled environments. Patient specimen samples sent to labs require time-sensitive preservation, transport, and handling. Lab results, assessments, and interpretations need to be transmitted to physicians promptly and, recently due to new regulations, made accessible to patients in secure, HIPAA-compliant formats. Further, no single laboratory provides every known laboratory service; thus, labs partner and collaborate with each other both regionally and nationally so that *all* laboratory services are ultimately available for patients.

To accomplish these feats with high quality reliability, lab facilities, personnel, and the tests they provide are highly regulated under a three part framework consisting of federal regulations under the Clinical Laboratory Improvement Amendments (CLIA), state laws, and accreditation by deemed authorities such as the College of American Pathologists. This regulatory framework requires both extensive validation and oversight to ensure quality of diagnostic services, yet allows laboratories the flexibility to develop and validate lab tests quickly and, thus, more quickly adopt new scientific knowledge and rapidly respond to unmet public health needs.

Operating this way, laboratory medicine and innovation, as we know it, allowed laboratories in the 80's and 90's to find, characterize, and keep pace with the rapidly mutating HIV virus so that drugs could be designed, their effectiveness measured, and the disease transformed from a death sentence to a more manageable condition. Laboratory medicine and innovation has provided greater certainty to managing chronic health risks and conditions such as stroke, heart disease, and diabetes. Laboratory medicine and innovation *is* allowing for breast and other cancers to be differentiated at the genetic and molecular level into multiple disease subcategories and, thus, allow physicians and patients to eliminate ineffective, unnecessary, even harmful treatments, and select more targeted therapies to better affect patient outcomes.

Like other health care sectors, the clinical laboratory industry faces pressure from all sides, whether for lower prices and less robust insurance coverage of services or whether from calls for increased, even duplicative oversight and overly cumbersome standards for introducing innovative new technology and medical knowledge. Unlike other health care sectors, however, laboratory services do not "act on" the patient and, in fact, the laboratory will often not even encounter the patient in-person. Whereas a drug is absorbed, a pace-maker inserted, or even a surgeon operates on the patient, the lab analyzes and quantifies samples *removed from* the patient so that these other, more direct health care interventions can be weighed, assessed, and decided upon by the physician and patient.

Grounded in our long history of innovation and commitment to patient care, ACLA looks forward to partnering with the Energy and Commerce Committee and other stakeholders to highlight the critical role of clinical laboratory services in increasing health care value and advancing innovation. We are committed to working with you to ensure patients have access to ever higher quality health care.

Sincerely,



Alan Mertz
President, ACLA

Energy and Commerce Committee White Paper: 21st Century Cures: A Call to Action American Diabetes Association Comments

On behalf of the 26 million individuals living with diabetes and the 79 million individuals with prediabetes, the American Diabetes Association (the Association) is grateful to Chairman Fred Upton, Representative Diana DeGette and the members of the House Energy and Commerce Committee for the opportunity to review “21st Century Cures: A Call to Action,” the first in a series of white papers in support of the Committee’s “A Path to 21st Century Cures Initiative.”

The Association commends Chairman Upton and Representative DeGette for leading this effort to help ensure that the United States can be the worldwide leader in biomedical innovation. We share your belief that the cycle of discovery, development, and delivery should be fostered. Supporting this cycle of innovation is in the best interest of patients and their loved ones, researchers, health care providers, our economy and society.

For the diabetes community, there are numerous reasons for greater investments in research, literally millions and billions. Most importantly, nearly 26 million Americans have diabetes today and an additional 79 million individuals have prediabetes. Every 17 seconds, someone in this country is diagnosed with diabetes. Today, 230 Americans with diabetes will undergo an amputation, 120 will enter end-stage kidney disease programs, and 55 will go blind from diabetes. In addition to the horrendous physical toll, diabetes is economically devastating to our country. A 2013 Association report found the annual cost of diagnosed diabetes has skyrocketed by an astonishing 41 percent over the last five years – from \$174 billion per year in 2007 to \$245 billion in 2012.

The white paper poses a broad range of questions regarding the cycle of discovery, development, and delivery. The focus of our comments in response to the report will center on biomedical research and innovative discovery. Specifically, the Association’s comments address the following questions in the first paragraph of the Discovery section of the white paper, including, “how can we make sure that the U.S. maintains its leadership role in research and discovery? How much of the contributions should come from public and private sources? How can public-private partnerships further the discovery process?”

Additionally, our comments also address the questions in the third paragraph of the Discovery section in the white paper regarding advances in translational research, specifically, “how can we best leverage advances in translational research, health information technology, and communications so that we can collectively “connect the dots” more quickly and start developing potential therapies and cures?” As additional white papers are circulated, the Association looks forward to providing additional feedback to the Committee as this important process moves continues.

Discovery

Maintaining Our Leadership Role in Discovery

The Association agrees that while global research and discovery is a positive development, the U.S. must maintain its leadership role. The white paper asks for input on how we can make sure that this is the case going forward. In response to this vital question, the Association believes that we must

collectively – government, private, and non-profit sectors – make a deeper investment in biomedical research if we are to remain at the forefront of the global discovery efforts, including spurring the breakthroughs needed to stop the diabetes epidemic.

The Association is doing its part to support and advocate for cutting edge research. Expanding the field of diabetes research to accelerate progress toward a cure and improved treatments for diabetes is a major organizational priority for the Association. The Association was founded in 1940 and has been funding innovative research since 1952. First, we are dedicated to expanding and advancing the field of diabetes research through support of the most impactful, transformational investigator - initiated research. For example, since the research program's inception in 1952, nearly 4,000 research projects have been funded and the Association has invested nearly \$675 million in diabetes research. Last year, there were more than 400 ADA-funded research projects, performed by 375 researchers at 145 leading research institutions throughout the country. In 2013, the Association awarded \$35.75 million to support a broad spectrum of research. The Association is pleased with and very proud of the quality and depth of the studies funded in the past as well as those currently being conducted.

The Association is committed to developing strategies to better support early career investigators in diabetes as a way to help maintain our country's leadership role in discovery. The Association is doing all that it can to help foster the young scientists interested in pursuing careers in diabetes research. We recognize that these efforts will require support for researchers at a number of key stages along the academic pipeline and we will continue to support promising scholars at the undergraduate, graduate, doctorate levels and in all stages of their professional careers to ensure the vitality of future diabetes research.

For example, our new Pathway to Stop Diabetes initiative will support creative scientists who are just starting their careers in diabetes research – or who are already established in another field but want to expand their focus to diabetes. Through individual awards of \$1.625 million over the course of five to seven years, the program will allow researchers to explore new ideas without the distraction of having to pursue additional grant support. With a goal of funding 100 diabetes researchers over the next decade, Pathway grants will provide crucial support to individuals focusing on innovative ideas and transformational approaches.

While the Association is doing its part to foster discovery in diabetes research, the federal government is an integral partner and leader in the pursuit of a cure for diabetes and, in the interim, better treatment and management options for the disease. The human and economic costs of diabetes are vast and devastating and require a comprehensive effort to surmount the epidemic. The federal government is uniquely positioned to provide the leadership and financial resources to spur the discoveries necessary to tackle diabetes and other diseases. Unfortunately, while progress has been made because of the federal investment in biomedical research, the attacks on biomedical and translational research funded by the federal government continue to threaten the U.S. position in research and discovery. Federal funding for biomedical research at NIH represents less than 1% percent of overall spending. Federal funding for diabetes research represents less than one-half of 1% percent of overall spending, despite diabetes taking more lives than breast cancer and HIV/AIDS combined. If our country is to remain at the forefront of biomedical discovery, a deeper and consistent investment by the federal government is mandatory. This investment will come back to the country in economic savings and a healthier America.

The two most significant sources of federal discretionary funding leading the way in diabetes discovery are the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the NIH, and the Division of Diabetes Translation (DDT) at the CDC. Together, DDT and NIDDK are working to alleviate the burden diabetes places on individuals and on our health care system. In light of the diabetes epidemic, there is every reason to deepen the investment in discoveries at NIDDK and DDT that will move us closer to preventing, better managing, and curing this horrific disease. While NIDDK drives diabetes-related biomedical discovery, it is important to note the essential role translational research, supported by DDT, plays in creating a pathway for the delivery of NIDDK innovation directly to those with, and at risk for, diabetes in the form of better diabetes prevention and management tools.

NIDDK-funded research is world-renowned. Examples of NIDDK-funded breakthroughs include: new drug therapies for type 2 diabetes; the advent of modern treatment regimens that have reduced the risk of costly complications like heart disease, stroke, amputation, blindness and kidney disease; and ongoing development of the artificial pancreas, a closed looped system combining continuous glucose monitoring with insulin delivery. However, the worldwide leadership role NIDDK has in diabetes research is jeopardized by the considerable ground lost due to funding reductions as well as the failure of overall funding to keep pace with biomedical inflation. NIDDK funding peaked in FY 2010, and has most recently suffered from the impact of across-the-board sequestration cuts due to the Budget Control Act of 2011. As a result, NIDDK has been unable to fund many promising grant applications, severely affecting the prospects for new and improved treatments and ultimately the discovery of a cure. A deeper investment in NIDDK would allow the restoration of sequestration cuts, enable NIDDK to support current research projects, and invest in additional studies that hold the promise of stopping diabetes.

Additional federal resources for NIDDK will also help ensure the Institute can continue to coordinate the nation's response to the epidemic, such as through its role as the convener of the Diabetes Mellitus Interagency Coordinating Committee, which ensures the NIH, CDC, Department of Veteran's Affairs, and other departments and agencies are working together to effectively and efficiency combat diabetes.

Investment in the CDC's DDT is also critical to spurring the innovation needed to stop the diabetes epidemic. DDT, which is a part of CDC's National Center for Chronic Disease Prevention and Health Promotion, leads efforts to prevent diabetes and its terrible complications. This includes developing and implementing prevention strategies and educational activities to address diabetes. An important component of these efforts is the work DDT undertakes to translate key diabetes research findings into practice, bringing more effective ways to prevent and treat diabetes. DDT's translational research efforts transform the wonderful work of the NIDDK into new and innovative approaches to diabetes in communities across the country.

The Role of Public-Private Partnerships

The white paper asks how much of the contribution toward maintaining a leadership role in discovery should come from public and private sources, and how public-private partnerships can further the discovery process.

The Association is always at the ready to collaborate with our partners in the federal government and in the private sector in the pursuit of new and better ways to address the diabetes epidemic.

While we cannot offer a specific ratio for public-private contribution towards maintaining U.S. leadership in discovery, we believe that partnerships between the federal government and private stakeholders have and should continue to play an integral role in fostering innovation. The federal government holds a leadership position in ensuring these partnerships maximize the intellectual capacity and financial resources federal agencies, industry, academic institutions, and non-profit organizations, including the Association, can bring to bear to tackle diabetes and other diseases. An example of a successful public-private partnership is the groundbreaking Diabetes Prevention Program (DPP), and the long-term follow up Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP, which was conducted by the NIDDK, found modest weight loss through dietary changes and increased physical activity could prevent or delay the onset of type 2 diabetes by 58 percent. Translating the clinical trial to a community setting showed these results could be replicated for a cost of about \$400 per participant. The Association was happy to co-support both studies. The National Diabetes Prevention Program at CDC follows this effective low-cost community model for reducing the rising epidemic of type 2 diabetes by ensuring the availability of low-cost, highly successful diabetes prevention programs in local communities across the country. Currently, over 500 organizations have applied for CDC recognition and there are 1,353 National Diabetes Prevention Program sites nationwide. In an additional example of public-private collaboration, many of these sites receive third party reimbursement from insurers such as United Health and employers. This success could not have happened without the significant leadership role and investment from the federal government.

Partnerships like the newly instituted Accelerating Medicines Partnership (AMP), which includes NIH, the Food and Drug Administration (FDA), ten biopharmaceutical companies, and several non-profit organizations, including the Association, are critical to the advancement of biomedical discovery. The goal of AMP – to develop new treatments for diseases by finding biological targets of disease most likely to respond to new therapies – is an important one. The Association is excited about being a part of this public-private partnership and looks forward to progress in identifying DNA regions critical for the development or progression of type 2 diabetes and to this information being used to advance the development and effectiveness of therapies.

Conclusion

Americans with, and at risk for, diabetes are counting on Congress to work with public and private stakeholders to foster biomedical discovery. We believe the best way to confront the advancing human and economic pain diabetes exacts on our country is with a deeper investment in medical research so that American remains the leader in innovation that will lead to cutting edge treatments and cures for the full spectrum of horrendous diseases, including diabetes. We stand ready to work with the Committee in this effort and we thank you for the opportunity to submit

comments on this white paper. Should members of the Committee and their staff have any questions or need additional information, please do not hesitate to contact Lisa Cox, Associate Director, Federal Government Affairs, at 703-253-4363, or lcox@diabetes.org.

