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IDSAs Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
EMAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

June 10, 2014

Representative Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515

Representative Diana DeGette
2368 Rayburn House Office Building
Washington, DC 20515

Submitted electronically to cures@mail.house.gov

RE: 2nd White Paper — 21st Century Cures: An Update on the President's Council of Advisors on Science and Technology 2012 Report on Propelling Innovation

Dear Chairman Upton and Representative DeGette:

On behalf of the Infectious Diseases Society of America (IDSAs), thank you for this second opportunity to comment on the 21st Century Cures Initiative. IDSAs shares your commitment to fostering greater drug innovation and development, particularly for urgently needed new antibiotics. We agree that many of the recommendations set forth in the President's Council of Advisors on Science and Technology (PCAST) 2012 Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation can inform the Committee's efforts to stimulate pharmaceutical research and development (R&D). Below we offer specific comments and recommendations about how the Committee can apply PCAST's recommendations to incentivize antibiotic R&D.

As IDSAs explained in our response to the 21st Century Cures first white paper, the rapidly increasing rates of antibiotic resistance and the nearly dry antibiotic pipeline constitute a public health crisis in need of urgent federal action. While the Generating Antibiotic Incentives Now (GAIN) Act has provided a valuable incentive, as evidenced by Roche recently re-entering antibiotic R&D, key stakeholders agree that much more must be done to rebuild the necessary antibiotic R&D enterprise to produce the variety of new antibiotics that patients desperately need to treat serious or life-threatening infections.

PCAST Recommendation: Support Federal Initiatives to Accelerate Therapeutics

IDSAs strongly agrees with the PCAST recommendation for increasing funding for the National Institutes of Health (NIH) to allow for new and further research on the underlying basis of disease and therapeutics. Sustained, robust funding is needed not only to spur research today, but also to encourage the younger generations to pursue careers in research to ensure the future of our nation's biomedical research enterprise. IDSAs urges the Committee to work with your colleagues on the Appropriations Committee and in congressional leadership to better prioritize funding for the NIH, and specifically the National Institute for Allergy and Infectious Diseases (NIAID).

Between Fiscal Year (FY) 1998 and FY 2003, Congress doubled the funding for NIH. Since that time, NIH has received very modest increases some years and even cuts in FY 2011 and FY 2013. For FY 2015, the President proposed a \$200 million increase for NIH. However, NIH estimated that the Biomedical Research and Development Price Index for 2015 would be 2.9%. As such, the 0.7% increase requested for NIH in the President's budget continues the 10-year downward trend in purchasing power at the NIH. The overall NIH grant success rate for FY 2013 is likely to be reported as falling to 15%, its lowest level in history. The latest funding line reported by investigators for investigator initiated grants (R01s) is the 9th percentile.

Depressed NIH funding is having a chilling effect on research, causing established researchers to scale back or completely discard promising research, lay off laboratory staff and dismantle research infrastructure that took years to build. Young people are so discouraged by the lack of NIH funding that they are abandoning potential careers in research entirely, seriously jeopardizing our nation's ability to remain a leader in biomedical innovation.

Weakened NIAID funding comes at a particularly problematic time as we are facing an onslaught of emerging, growing and re-emerging infectious disease threats for which patients need researchers to help develop cures. In addition to infections caused by multi-drug resistant pathogens, U.S. patients have now experienced our first cases of the Middle East Coronavirus (MERS). Dengue and chikungunya are becoming more prevalent. We are also seeing a resurgence of measles. College campuses are struggling with meningitis cases. Of course seasonal and pandemic influenza remain a serious concern.

In the area of infectious diseases, we are facing urgent needs and opportunities that require a well-funded NIH in order to advance scientific discovery in life-saving ways. IDSA specifically supports increased funding for NIAID, which funds a variety of critical infectious diseases research efforts. For example, the NIAID recently established the [Antibacterial Resistance Leadership Group \(ARLG\)](#) 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. If properly supported, the ARLG is well poised to help catalyze efforts to bring new antibiotics to patients.

While the PCAST report does not focus on the need to increase funding for the Centers for Disease Control and Prevention (CDC), IDSA argues that strong funding for this agency is equally important. CDC has an important role in research and innovation. 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. Unfortunately, CDC funding has suffered dramatic cuts in the last several years—most notably a \$740 million cut in FY 2011 and an additional \$300 million cut in FY 2013 due to sequestration.

PCAST Recommendation: Catalyze the Creation of a Broad-Based Partnership to Accelerate Therapeutics

IDSA wholeheartedly agrees with PCAST’s assessment that a high-level public private partnership (PPP), with representation from the federal government, academia, industry, physicians and other key stakeholders, is needed to promote innovation and improvement in the discovery, development, and evaluation of new medicines for important public health needs. As PCAST correctly asserts, this mission cannot be appropriately performed by existing federal entities. Given the urgent need for new antibiotics, and the significant scientific, economic and regulatory challenges these products face, these areas are well suited for a PPP to tackle. The European Commission (EC) has a successful PPP that should serve as a strong example for the U.S.

In 2012, the EC launched their ground-breaking New Drugs For Bad Bugs (ND4BB) 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 U.S. has begun recognizing the importance of PPPs for antibiotic 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. However, discreet projects, while valuable, will likely not yield as powerful an impact as a large-scale, well-coordinated PPP similar to the ND4BB initiative.

IDSA urges U.S. 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 have noted that government initiative was vital to the creation of these valuable partnerships.

PCAST Recommendation: Create a New Pathway for Initial Approval of Drugs Shown to be Safe and Effective in a Specific Subgroup of Patients

IDSA urges the Committee to swiftly act upon the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, which would follow PCAST’s recommendation to establish a new approval pathway for new antibiotics to treat infections that are resistant to current available treatments. Under ADAPT, 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 European Union is already developing regulatory schemes to allow for this type of limited population antibacterial drug development, and we strongly urge the U.S. to follow suit.

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.

The ADAPT Act would speed patient access to desperately needed, life-saving new antibiotics and antifungals, 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 ADAPT drugs to make it as simple as possible for the health care community (including those conducting educational campaigns, such as the CDC Get Smart program) to easily recognize that these drugs have been approved in a different manner than traditional antibiotics and must be used appropriately. As PCAST noted, a limited population drug approval pathway must be implemented in such a way as to strongly influence behavior. Lastly, a visual element would help give the Food and Drug Administration (FDA) the comfort level it needs to approve new drugs under this pathway, thus increasing the potential success of the ADAPT Act in bringing lifesaving new antibiotics to patients. We believe this issue can be easily addressed as the legislation moves forward.

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. Given the urgent need for new antibiotics and the broad stakeholder support for a limited population antibacterial drug pathway, we believe that the ADAPT Act should move forward right away.

PCAST Recommendation: Improve FDA's Tools for Monitoring and Communication of Clinical Benefits and Risks

IDSA has long called for data on antimicrobial drug use to be collected in real time and made publicly available on a regular basis. PCAST specifically recommended that Congress increase FDA funding to expand post-marketing surveillance activities, such as the Sentinel System, to better identify and evaluate the potential benefits and risks of drugs and the populations at highest risk for adverse events. IDSA agrees with the potential value of Sentinel, and would also alert the Committee to another important, but underfunded, tool for monitoring antimicrobial drug use and resistance rates — CDC's National Healthcare Safety Network (NHSN). NHSN's antibiotic use module and antibiotic resistance module provide important opportunities for collecting critical data. But NHSN has been flat funded for years, despite repeated requests from the Administration for funding increases. Additional support for this program would allow and encourage more healthcare facilities to report important antibiotic use and resistance data through NHSN. IDSA urges the Committee to authorize funding in this area and to work with

your colleagues on the Appropriations Committee and in congressional leadership to provide more robust resources for antimicrobial use and resistance monitoring and data collection.

While the FDA Sentinel System and other programs, such as the Antibiotic Use and Antibiotic Resistance modules of CDC's NHSN provide valuable data and should be better funded in order to expand their reach, the U.S. still lacks a comprehensive system for collecting in real time data on antimicrobial drug use and resistance rates. Specific data on the type and quantity of antimicrobial drugs used in patient care are needed, not only to evaluate effectiveness and identify adverse outcomes (key areas of focus for Sentinel), but also to determine antimicrobial drug overuse patterns and their impact on the development of resistance. Only by understanding the scope and severity of the problem can we develop, implement and evaluate effective interventions to prevent and control resistance. Regarding antimicrobial drug use data, at a minimum IDSA recommends collection of the following data: specific drug, indication, site of infection, organism, basic patient demographics, treatment duration, and outcomes (efficacy and side effects).

As the Committee considers PCAST's recommendation regarding the Sentinel System, IDSA urges you to consider the European Union's (EU) successful system across all member countries for collecting antimicrobial drug use data and tracking antimicrobial resistance trends. The European Surveillance Antimicrobial Consumption (ESAC) and the European Antimicrobial Resistance Surveillance Network (EARS-Net) are funded by the European Centre for Disease Control (ECDC) and serve as a strong example of the type of comprehensive data collection needed in the U.S.

PCAST Recommendation: Reform Management Practices at FDA

IDSA agrees with PCAST's recommendations that FDA seek to make the approval process for drugs more transparent, predictable, responsive, and efficient through a variety of means including addressing regulatory barriers, advancing regulatory science and issuing guidance documents in a timely manner that is in accordance with national priorities.

IDSA strongly supports collaborative regulatory science efforts underway among FDA, NIAID and the Foundation of the NIH (FNIH) along with industry and academia to develop new endpoints for antibacterial drug trials, as well as the Clinical Trials Transformation Initiative (CTTI), established by Duke University and the FDA to engage patients and experts in discussions of current practices and challenges in the design and conduct of antibiotic trials and to develop novel approaches to overcome these challenges.

IDSA has long called for clear and feasible regulatory guidances for antibiotic clinical trials. In setting regulatory guidance for antibiotic development, FDA must balance the public health risks of approving a potentially less effective drug with the risk of having no new, critically needed antibiotic available to treat patients infected with resistant pathogens. While significant work remains, we note that FDA has made recent progress in this area. In 2013, FDA sought public comment on new approaches to antibacterial drug development, and specifically requested input on prioritizing new and updated clinical trial guidance documents. Also in 2013, FDA published

draft guidance for industry on antibacterial therapies for patients with unmet medical need for the treatment of serious bacterial diseases. [IDSA offered comments](#) on this draft guidance which overall was thoughtful and provided useful information that we hope will stimulate more antibacterial drug development. FDA also published draft guidance for industry on pulmonary tuberculosis (TB): developing drugs for treatment in 2013. In light of the urgent need for new drugs to treat TB, particularly drug-resistant TB, this guidance provides much-needed clarity for sponsors interested in TB product development. FDA has continued its progress this year, issuing draft guidance on community-acquired bacterial pneumonia: developing drugs for treatment. [IDSA noted](#) that this document was a good faith effort by FDA to address concerns raised about previous guidance documents, but additional changes are needed, including allowing a greater percentage of patients with prior antibacterial drug therapy, expanding the non-inferiority margin in certain circumstances, and providing greater clarity on multiple issues.

PCAST Recommendation: Study Current and Potential Economic Incentives to Promote Innovation in Drug Development

PCAST correctly asserts that current economic incentives are insufficient to meet the need for new antibiotics to treat infections caused by drug-resistant bacteria. However, IDSA disagrees with PCAST's recommendation to study incentives for antibiotic R&D. Numerous studies on this issue have already been commissioned and completed. Real world experience, including widespread company exits from the antibiotic market over the last few decades and a sharp decline in FDA approvals of new antibiotics, clearly demonstrate a market failure and the need for new incentives. Numerous factors make antibiotics an unattractive economic prospect for companies: Antibiotics are typically priced low compared to other products, taken for a short duration, and held in reserve to protect against the development of resistance.

The Committee recognized the need for Congress to incentivize antibiotic R&D in 2012 when it led the successful effort to enact the Generating Antibiotic Incentives Now (GAIN) Act. As IDSA and other key stakeholders have asserted, the GAIN Act was a critical first step, but more work remains to sufficiently stimulate antibiotic R&D. Waiting for the results of another study to once again demonstrate the need for antibiotic incentives will waste valuable time, and patients will continue dying as they wait for desperately needed new antibiotics.

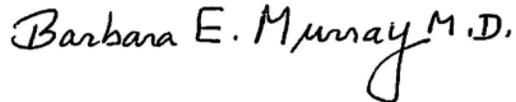
IDSA urges you to continue developing and advancing policies to stimulate antibiotic R&D and recognizes this effort may include collaborative work with colleagues on other committees (particularly Ways & Means and Appropriations). For example, reimbursement mechanisms can be used to help stimulate antibiotic 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. Strong communication between the Centers for Medicare and Medicaid Services (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 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 antibiotic R&D through NIAID, BARDA, CDC, the Defense Threat Reduction Agency (DTRA), and the Defense Advanced Research Projects Agency (DARPA).

Again, IDSA thanks you for this opportunity to comment. The Society is eager to maintain an ongoing dialogue with you regarding the 21st Century Cures Initiative and policies to incentivize antibiotic R&D. If you would like any additional information, or if IDSA can assist you in any way, please contact Jonathan Nurse, IDSA's Director of Government Relations, at jnurse@idsociety.org or 703-299-0202.

Sincerely,

A handwritten signature in black ink that reads "Barbara E. Murray M.D." The signature is written in a cursive style with a large, looped initial 'B'.

Barbara E. Murray, MD, FIDSA
President