IDSA 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

IDSA
Infectious Diseases Society of America

May 30, 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: 1st White Paper — 21st Century Cures: A Call to Action

Dear Chairman Upton and Representative DeGette:

On behalf of the Infectious Diseases Society of America (IDSA), 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 IDSA 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.

IDSA is advocating for new antibiotics and diagnostics to improve and save the lives of the many patients who are suffering from serious or life-threating 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 Jonathan Nurse, IDSA's Director of Government Relations, at jnurse@idsociety.org or 703-299-0202.

Sincerely,

Barbara E. Murray M.D.

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)