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IDSA
Infectious Diseases Society of America

June 13, 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: 3rd White Paper — 21st Century Cures: Patients

Dear Chairman Upton and Representative DeGette:

On behalf of the Infectious Diseases Society of America (IDSA), thank you for your continued efforts regarding the 21st Century Cures Initiative and multiple opportunities to comment. IDSA recognizes that this third white paper focused on patients' perspectives, and we appreciate the Committee seeking out this important voice. Over a decade ago, IDSA launched policy efforts to address antibiotic resistance and the need for new antibiotics on behalf of our increasing numbers of patients who were contracting and dying from multi-drug resistant infections that we could not effectively treat with existing therapies. Unlike many chronic conditions, there are no large, well-organized groups able to advocate on behalf of patients who suffer from serious or life-threatening infections that are resistant to current antibiotics.

In the past decade, rates of resistance have continued to climb, as have the numbers of patients contracting and dying from infections caused by resistant pathogens, as IDSA has noted in our previous comment letters regarding this initiative. Thus, IDSA has intensified our commitment to advance policy solutions to spur the development of the new antibiotics needed to save our patients' lives.

IDSA spotlights examples of the patients for whom we advocate on our website, including children, adults and seniors who have lost their lives or suffered devastating health outcomes due to resistant infections. For example, you can read the story of 17-year-old Rebecca Lohsen, a healthy high school honor student and swimmer from New Jersey who died of an MRSA infection. Sadly, these stories are a small sampling of the millions of people in the U.S. who struggle with resistant infections and have few or no satisfactory treatment options. With these patients in mind, IDSA offers the following recommendations in response to the questions raised in this third white paper.

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

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.

Antibiotic research and development (R&D) has plummeted 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. Companies are lacking sufficient incentives to develop new antibiotics and must answer to stockholders. 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 used over years to treat chronic diseases. 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 with no guarantee that even one will make it to the market, particularly given that the failure rate of bringing drugs at this stage to the market is very high.

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

In response to IDSA's advocacy about patients' desperate need for new antibiotics, Congress and various federal agencies have taken initial steps to foster antibiotic R&D. But key stakeholders agree that more must be done/much more be done. … much more is needed?. In 2012, the Committee led successful congressional efforts to enact the Generating Antibiotic Incentives Now (GAIN) Act, which provides an additional 5 years of exclusivity for antibiotics and antifungals that treat serious or life-threatening infections. This legislation was an important first step in revitalizing our nation's antibiotic R&D enterprise.

The National Institute for Allergy and Infectious Diseases (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. In addition to helping to develop new cures, ARLG research can also help determine the best way to use existing antibiotics to maximize their potential to cure patients and save lives. If properly supported, the ARLG is well poised to help catalyze efforts to bring new antibiotics to patients and reduce the disease burden associated with drug resistant pathogens.

The Biomedical Research and Development Authority (BARDA) is also a critical source of funding for new antibiotics. In the last few years, BARDA has awarded contracts to multiple large and small pharmaceutical companies to develop new antibiotics to treat serious threats, including infections caused by gram negative bacterial pathogens, hospital acquired pneumonia, complicated urinary tract infections, and infections caused by carbapenem-resistant

Enterobacteriaceae (CRE)—infamously termed the "nightmare" or "urgent threat" bacteria by the Centers for Disease Control and Prevention (CDC) Director Tom Frieden. Products supported by BARDA funding have potential use not only in bioterror situations, but also in more traditional healthcare settings.

While these important initiatives are all critical in helping to revive the stagnant antibiotic pipeline, they are not sufficient to thoroughly revitalize antibiotic R&D. Recent federal budget pressures have put serious funding constraints on all federal agencies, including NIH and BARDA, severely limiting the reach of these agencies' efforts.

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

The National Institutes of Health (NIH) is the driver for a significant portion of basic research in the U.S. New infectious diseases are regularly emerging, and existing pathogens continuously mutate and require additional research to understand the best way to treat infected patients. Congress can best incentivize the necessary basic research by providing the NIH with sufficient funding for them to meet the important missions of its institutes.

Robust, sustained 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. IDSA 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 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 basic 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.

Congress also has a critical role in fostering research that can prevent disease, including infections caused by rare or emerging pathogens about which we still know relatively little. For example, IDSA urges the Committee to help the Centers for Disease Control and Prevention (CDC) conduct greater research on novel strategies, best practices and evaluation of methods to prevent, control and eradicate antibiotic resistant organisms. CDC's prevention EpiCenters (a partnership with academic investigators) conduct valuable work in this area regarding healthcare associated infections, but flat funding over the last several years is preventing these collaborations from expanding their critical work. CDC's proposed Detect and Protect Against Antibiotic Resistance initiative, which has broad support, would also establish regional prevention collaboratives. These are envisioned to be groups of healthcare facilities in communities across the country that work together to implement and evaluate best practices for antibiotic prescribing and preventing infections. This initiative will also improve antibiotic stewardship by evaluating state-to-state variations in antibiotic prescribing and implementing best practices for antibiotic prescribing. IDSA believes that every healthcare facility should have in place an antibiotic stewardship program to help guide appropriate use. By reducing the overuse and misuse of antibiotics, we can slow the rate at which resistance to these drugs develops, and thus extend the longevity of these drugs' ability to cure patients.

IDSA also urges the Committee to work with your colleagues on the Appropriations Committee to ensure strong funding for CDC. 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.

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

While the NIH funds critical basic research, and some extremely important clinical research through efforts such as the ARLG, Congress must incentivize industry to re-enter antibiotic R&D to ensure that desperately needed new antibiotics are developed and brought to patients. The GAIN Act was a vital first step, but Congress must now build on that foundation.

IDSA recognizes this effort may include collaborative work with colleagues on other committees (particularly Ways & Means and Appropriations). For example, reimbursement mechanisms hold important potential 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 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 and antifungal 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, BARDA, the Centers for Disease Control and Prevention (CDC), the Defense Threat Reduction Agency (DTRA), and the Defense Advanced Research Projects Agency (DARPA). 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 (mentioned above) 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 can we learn from your experiences with clinical trials and the drug development process?

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 swiftly act upon the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, which would 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.

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 antibiotic drugs 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.

Importantly, if the U.S. government does not make it feasible for companies to conduct antibiotic clinical trials in the U.S., companies will conduct these trials in other countries with different pathogens and different methods and/or standards of care. Such activities could leave patients in the U.S. still in need of life-saving new drugs.

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

Antibiotics are experiencing a market failure, meaning that market forces alone are not sufficient to incentivize companies to develop new antibiotics due to the significant economic and regulatory barriers discussed above. In previous similar situations in which the market failed to yield products desperately needed by patients, such as with orphan drugs, the government took decisive actions to address the market failure in the interest of patients. For example, the government can enact many policies (enhanced exclusivity, improved reimbursement, targeted tax credits) to provide economic incentives to companies to conduct desperately needed R&D in areas where significant economic barriers exist. In many instances, the NIH funds research that the private sector is unable or unwilling to conduct. But Congress must ensure that NIH receives robust funding to meet this need.

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

In setting regulatory guidance for antibiotic development, IDSA has strongly urged the Food and Drug Administration (FDA) to balance the public health risks of approving a potentially less effective drug with the risk of having no new, critically needed antibiotics available to treat patients infected with resistant pathogens. While recent FDA clinical trial guidances demonstrate some progress in this area, more work remains.

Already conservative estimates of antimicrobial efficacy relative to placebo/no therapy should not be further "discounted" when setting requirements for non-inferiority margins for clinical trials, as discounting results in excessively large trial (and thus often infeasible) requirements. The treatment effect of antibiotic therapy for serious and life-threatening infections is very large. The primary issue in justifying the non-inferiority margin for a clinical trial is determining how

much of the clinical benefit of antimicrobial therapy must be preserved, which should be based upon an assessment of the relative merits of the specific experimental drug versus currently available therapy. Qualified experts in clinical medicine, who care for patients and know the current challenges and needs for improving treatment, possess the expertise required to define how much of a potential decrease in treatment benefit can be justified as a trade-off against the critical need to develop new efficacious and safe drugs and have them available for clinical use.

Earlier this year, FDA published a draft guidance for industry on developing drugs to treat community acquired bacterial pneumonia, which is an important cause of significant morbidity and mortality in the U.S., particularly among young children and the elderly. IDSA recognized that the draft guidance was a good faith effort to improve upon previous agency guidance in this area. However, IDSA remains concerned about the FDA's selection methodology for non-inferiority (NI) margins. Compelling evidence indicates that there is a real effect of antimicrobial therapy on both death as well as on speed of recovery. The current proposed NI margin of 12.5% is a significant improvement over past proposals. However, IDSA further recommends that consideration be given to expanding the NI margin to 15% under special circumstances. A margin of 15% could be justified if, for example, the study drug has other critically important advantages, such as better safety, better tolerability, shorter treatment duration, or activity against multidrug-resistant pathogens with limited available treatment options.

In short, as new antibiotics are critically needed, we must balance feasibility of conducting studies (and the resultant public health benefit of facilitating approval of effective new antibiotics) against a desire to narrow the non-inferiority margin. While patients may be harmed if less effective drugs are allowed to reach the market, they also may face even greater harm if they have an infection for which no effective antibiotics have been developed. Furthermore, if the criteria for trial conduct are so strict that it is not feasible to enroll meaningful numbers of patients in the US, we run the risk that the observed safety and efficacy of the drug in its pivotal studies will not be informative regarding the safety and efficacy of the drug for patients in the US who are treated with the drug. The key is to create a regulatory path that balances these competing risks.

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

IDSA firmly believes 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 the discovery, development, and evaluation of new antibiotics. There is an urgent unmet medical need for new antibiotics, and antibiotic R&D faces significant scientific, economic and regulatory challenges. 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 U.S. 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.

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

The Committee is largely responsible for one of the most compelling success stories in the area of antibiotic R&D—the GAIN Act, mentioned above. This important first step has encouraged companies to consider re-entering the antibiotics market, not only because it provides an additional 5 years of exclusivity for new antibiotics to treat serious or life-threatening infections, but also because it demonstrates to industry that Congress is committed to the urgent public health need for new antibiotics. To ensure greater and continued success, Congress must build upon the GAIN Act by enacting additional incentives, as discussed above.

The European ND4BB initiative, also discussed above, is a best practice that the Committee can leverage by authorizing a similar effort in the U.S.

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

The medical and societal costs of antibiotic resistant infections are significant. A study published in 2009, "Hospital and Societal Costs of Antimicrobial Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship," extrapolated that resistant infections result in an additional $35 billion in healthcare and societal costs and an additional 8 million hospital days.

Better, more effective antibiotics will allow patients to be cured more rapidly, decreasing hospital admittance and length of stay. Faster cures can also limit the need for other costly interventions, including administration of less effective drugs, surgeries and physical therapy. Safer antibiotics can also reduce harmful side effects, such as kidney failure, that result in the need for additional costly treatments. Most importantly, more effective, safer antibiotics save

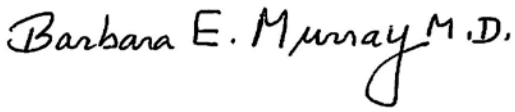
lives and improve the quality of life for patients.

How can Congress help?

As noted above, Congress can help patients by fostering the development of desperately needed new antibiotics. Congress can build upon the success of the GAIN Act to further reduce the economic and regulatory barriers facing antibiotic R&D using the specific recommendations discussed above.

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,



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