

“21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development”

Responses to Questions for the Record Dr. Barbara Murray Infectious Diseases Society of America (IDSA)

The Honorable Joseph R. Pitts

- 1. What are other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?**

In 2012, the European Medicines Agency (EMA), the European Union’s (EU) equivalent to our Food and Drug Administration (FDA), released a guidance document¹ on antibiotic development that included a focus on the development of new antibiotics to treat serious or life-threatening infections that occur in small numbers of patients and for which there is an unmet medical need. It is important to develop drugs to treat these infections before they sicken larger numbers of people yet development is challenging because when a resistant pathogen infects only a small number of people, it is not feasible to conduct a large clinical trial. The EMA addressed this regulatory barrier by permitting companies to study new antibiotics to treat such infections in smaller clinical trials. The limited population approach makes it possible for companies to study and bring to market some of the most urgently needed new antibiotics for patients who currently have few or no safe and effective treatment options.

The bipartisan Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, would establish a similar limited population antibiotic development approval pathway in the U.S. in which companies could study in smaller clinical trials new antibacterial or antifungal drugs to treat serious or life-threatening infections for which there is an unmet medical need. ADAPT drugs would receive approval just for the limited population in most need of the therapy, as opposed to all patients. Smaller clinical trials are also less costly, which is an important consideration given the economic hurdles still facing antibiotic research and development (R&D). Enacting ADAPT will enable urgently needed antibiotic development more rapidly than is now possible through existing FDA regulations. Further, the ADAPT Act also includes several provisions to help guide the appropriate use of these drugs. One half of Energy and Commerce Committee members have cosponsored the ADAPT Act, and the legislation enjoys broad

¹ European Medicines Agency, “Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 REV 2) to address indication-specific clinical data,” June, 2012, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129443.pdf

support among medical societies, public health organizations and industry.² The President's Council of Advisors on Science and Technology (PCAST) has also endorsed this approach in its 2014 Report to the President on Combating Antibiotic Resistance.³

Also 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 this program is to develop strong 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 support for ND4BB (approximately \$300 million for the first phase) was nearly equally split from government and industry sources.

IDSA recommends that the US establish a similar, complementary PPP, using the ND4BB model. We are encouraged by the recent National Strategy for Combating Antibiotic Resistant Bacteria (CARB), released by the White House on September 18, 2014, which lists as an objective the creation of a biopharmaceutical incubator.⁴ The incubator is described as a consortium of academic, biotechnology and pharmaceutical industry partners to promote innovation and increase the number of antibiotics in the drug-development pipeline. While we have not yet seen any details about how the incubator would be established or operated, we believe this proposal holds significant promise. It should help incentivize research among industry and academic laboratories. Our understanding is that the key limitation for moving forward with this incubator proposal is the need for increased appropriations for the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health (NIH). Thus, while it is not within this Committee's jurisdiction per se, we hope that you would be willing to weigh in with your colleagues regarding its importance.

In July 2014, United Kingdom (UK) Prime Minister David Cameron announced the establishment of a high level international assessment committee (headed by Jim O'Neill, the former chief economist at Goldman Sachs) to consider how governments can effectively incentivize industry to develop new antibiotics and how to best encourage the appropriate use of antibiotics, especially in poorer countries. IDSA recommends that the US support these global activities. But we also recognize that many thoughtful expert reports have already made recommendations regarding the variety of economic and

² Infectious Diseases Society of America, "ADAPT support letter," February, 2014, http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20/Letters/To_Congress/ADAPT%20group%20sign%20on%20letter%20FINAL.pdf

³ Executive Office of the President, President's Council of Advisors on Science and Technology, "Report to the President on Combating Antibiotic Resistance," September, 2014, http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf

⁴ The White House, "National Strategy for Combating Antibiotic-Resistant Bacteria," September, 2014, http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf

regulatory incentives needed to spur antibiotic development; including the ADAPT Act, tax credits, reimbursement reform, and additional funding for key federal agencies; and we urge Congress to quickly advance these policies and not wait for additional reports.

The Honorable Marsha Blackburn

- 1. Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21st Century Cures effort we'll put additional incentives in place for antibiotics that are designated as Qualified Infectious Disease Products (or QIDPs). What other specific incentives do you recommend Congress consider for FDA designated QIDPs?**

IDSA appreciates the strides in antibiotic development made possible by the GAIN Act and wholeheartedly agrees that additional incentives are urgently needed. The antibiotic pipeline remains quite tenuous and patients are continuing to die from antibiotic resistant infections because we lack the new antibiotics needed to safely and effectively treat them. To enact the array of incentives that we believe are necessary, multiple Congressional committees will need to act, beyond just the informed health experts of the Energy and Commerce Committee.

Strengthen the Mission of the Biomedical Advanced Research and Development Authority (BARDA)

In December 2006, the Energy and Commerce Committee and others worked to ensure enactment of the Pandemic and All-Hazards Preparedness Act (PAHPA), Public Law No. 109-417, which has broad implications for the Department of Health and Human Services' (HHS) preparedness and response activities. Among other things, the Act amended the Public Health Service Act to provide new authorities for a number of programs, including the advanced development and acquisitions of medical countermeasures or the Biomedical Advanced Research and Development Authority (BARDA).

In 2010, BARDA established a Broad Spectrum Antimicrobials (BSA) Program to focus on developing novel antibiotics to address biological threats as well as the public health threat of antibiotic resistance. In four years, the BARDA program has grown from supporting one industry partnership with an antibiotic candidate in Phase 2 development to six partnerships with three industry partners in Phase 3 clinical development. Since 2010, BARDA has awarded over \$550 million to companies for antibiotic development.

In its September 2014 Report to the President on Combating Antibiotic Resistance, the President's Council of Advisors on Science and Technology (PCAST) strongly recommended that BARDA's antibiotic development program be expanded beyond projects justified by security/bioterrorism considerations to include antibiotics that meet urgent public health priorities that are not traditionally defined as material threat agents. **It would be helpful for the Energy and Commerce Committee to clarify BARDA's**

mission to make explicitly clear that the agency should support the development of antibiotics that meet urgent public health priorities.

Federal Funding

IDSA agrees with the PCAST report's assertion that significant new federal funding will be needed to support antibiotic research and development (R&D). Specifically PCAST recommended:

- An additional \$150 million per year for the National Institutes of Health (NIH), the Defense Advanced Research Projects Agency (DARPA), and the Defense Threat Reduction Agency (DTRA) to support antibiotic resistance research. Federal agencies are important sources of funding for academic researchers in this space. IDSA urges that some of this funding be directed to the Antibacterial Resistance Leadership Group (ARLG), which was founded by the National Institute of Allergy and Infectious Diseases (NIAID) to develop, design, implement, and manage a clinical research agenda to increase knowledge of antibacterial resistance. The ARLG is focusing on antibacterial drug and diagnostic development, optimal usage strategies, infection control and other activities to limit the development of resistance.
- \$25 million per year to begin, with additional funds in the future, to establish the necessary infrastructure for a public private partnership (to be jointly administered by BARDA and NIH) and to pursue the development of a master clinical trials protocol (to be led by the NIH and the Food and Drug Administration or FDA).
- \$400 million for BARDA to support antibiotic development and \$400 million for BARDA to provide advance market commitments (AMC) and milestone payments as incentives for bringing a new antibiotic to market.

Tax Credits to Promote Antibiotic R&D

Economic experts agree that a combination of “push” and “pull” incentives are needed to effectively stimulate antibiotic R&D. The GAIN Act provides a valuable “pull” incentive (additional exclusivity). Improving reimbursement for the most urgently needed new antibiotics would be another important pull incentive. While not within the Energy and Commerce Committee's jurisdiction, we hope that Congress will also provide targeted tax credits for antibiotic R&D. Tax credits would provide an extremely valuable “push” incentive and would be a very important complement to other efforts undertaken by this Subcommittee. IDSA has developed a proposal to provide a credit of 50 percent of the qualified clinical testing expenses (which we would define as expenses incurred in phase 2 and 3 clinical trials) for new antibiotics and antifungal drugs to treat serious or life-threatening infections—the very same drugs eligible for the additional 5 years of exclusivity under the GAIN Act (life-saving new drugs that this Subcommittee deemed worthy of federal investment). 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.

Reimbursement Reform

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. This bill, which has been jointly referred to the House Ways and Means Committee and the House Energy and Commerce Committee, 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 and medically appropriate and consistent manner that provides companies with the certainty and predictability they need in order to develop life-saving new antibiotics or other novel life-saving therapies to treat serious or life-threatening infections. It is also very important to monitor the use of antibiotics that receive this increased reimbursement.

Congress may also wish to consider new policies that would significantly alter the way in which we pay for antibiotics, such as “delinkage” models that would de-link antibiotic reimbursement from antibiotic use by engaging in advance purchase contracts or by offering a prize or similar lump sum payment for licensing rights once the product is brought to market. Delinkage policies would clearly define the economic reward for antibiotic developers and help ensure good stewardship. The above mentioned PCAST report on antibiotic resistance discusses two potential approaches to delinkage for policymakers' consideration, summarized below:

Complete Delinkage

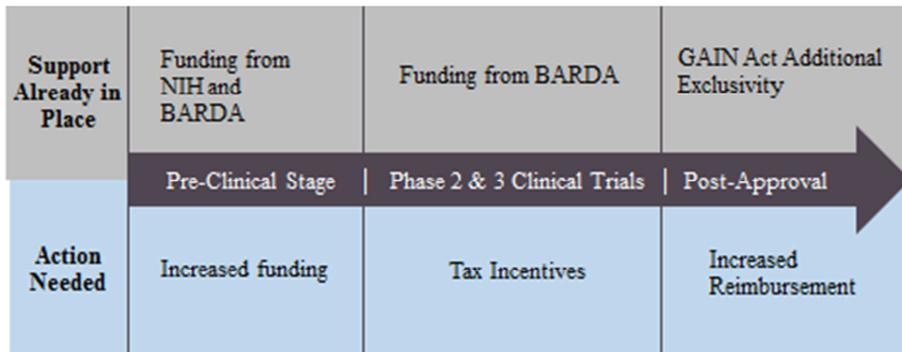
In this model, a drug developer might receive from the federal government (possibly through BARDA) a one-time lump sum payment that serves as a patent buyout and reward for bringing a new antibiotic to market. BARDA, or another appropriate federal agency, could contract with the drug company to produce the antibiotic as needed, and limit clinical use to specific circumstances and certain pre-defined conditions. Under complete delinkage, PCAST estimates that buyouts in the range of \$1 billion might be required.

Partial Delinkage

Under this model, a drug developer would receive a reward for developing the drug and would sell the drug, but would agree to certain stewardship requirements. BARDA has used such rewards successfully to incentivize the development of medical countermeasures to bioterrorism threats. An Antibiotic Incentive Fund (AIF) could be established under BARDA to provide advance market commitments and milestone payments as incentives for bringing a new antibiotic to market. The advance market commitment could be structured to secure the market availability of a given number of doses per year, determined by projected demand, over a given number of years, at a specified price. As a condition of receiving a payment from the AIF, industry partners could be required to develop and implement stewardship plans and apply other considerations (e.g., patent buyouts, restricted marketing, royalty payments, pricing

discounts, etc.). According to PCAST’s analyses, incentive payments in the range of \$400 million per drug would likely be required.

The chart below helps demonstrate the types of financial support needed throughout the antibiotic R&D process.



- 2. Congress via GAIN gave FDA a very important tool, to designate certain anti-infectives as Qualified Infectious Disease Products (QIDP): and the agency has made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should—real incentives are needed—we must avoid a situation where there’s confusion and differences over what qualifies for which type of incentive across different agencies of HHS. Will you respond to this statement?**

IDSAs completely agree that additional incentives are needed for antibiotic R&D. While GAIN has helped generate important progress, experts agree that the antibiotic pipeline remains fragile. As Congress creates incentives, it is also very important that the government effectively communicates to companies what incentives are available for particular products. For the sake of simplicity, when appropriate, Congress should apply new incentives to products that receive the Qualified Infectious Diseases Products (QIDP) status. For example, IDSAs propose providing a new tax credit for QIDPs. Because the proposed tax credit could be utilized during costly phase 2 and 3 clinical trials, it would be a strong complement to the increased exclusivity provided through the GAIN Act, from which companies derive a benefit after the drug has been brought to market.

However, there are instances in which it is in the best interest of patients to apply a new incentive to a narrower category of new antibiotics than QIDPs. The first example would be the Antibiotic Development to Advance Patient Treatment (ADAPT) Act, H.R. 3742, which would establish a limited population antibiotic approval pathway. IDSAs are very grateful that you are an original cosponsor of this important bill. As you know, the ADAPT Act would address a key regulatory barrier to the development of certain new antibiotics — the inability to populate a traditional, large scale clinical trial because the targeted infection is currently occurring in too few patients. Under ADAPT, companies could study these new antibiotics in smaller, less costly clinical trials, and must still demonstrate the drugs’ safety and effectiveness under FDA’s current evidentiary

standards. ADAPT drugs would be approved for a limited population. ADAPT includes several provisions to help guide the appropriate use of these drugs. Because ADAPT drugs would be studied in smaller trials, a greater amount of uncertainty regarding these drugs' risks would exist, as compared to antibiotics studied and approved through a more traditional pathway. Instead, Representatives Gingrey and Green, the authors of both GAIN and ADAPT, appropriately crafted ADAPT to apply only to drugs meeting an unmet medical need for a limited population of patients—i.e. those patients who could tolerate a greater amount of uncertainty because they do not have other viable treatment options and for whom drugs could not be developed using a traditional approval pathway.

IDSA believes that improving reimbursement for the most urgently needed new antibiotics would be another important pull incentive. In order to best meet the most urgent needs of patients, it may be most appropriate to target increased reimbursement for antibiotics to treat serious or life-threatening infections for which we have few or no safe or effective treatments. Only some QIDPs and Qualifying Pathogens under GAIN would meet this additional criterion. For example, Carbapenem-resistant *Enterobacteriaceae* (CRE) is a type of gram-negative bacteria — a category of highly resistant pathogens that cause deadly infections. It is resistant to all or nearly all existing antibiotics, and half of patients who contract a bloodstream infection from this germ die. Of the four new antibiotics that received FDA approval this year, none target gram-negative bacteria. It is extremely difficult and costly to develop antibiotics effective against gram-negative bacteria, in part because the outer layers of their cells (including cell walls and membranes) block drugs from getting into the cell. For antibiotics that address unmet medical needs, such as those to treat gram-negative infections or other gram-positive infections identified as urgent or serious threats, it is clear that additional incentives beyond those applied to all QIDPs, such as increased reimbursement, are needed to help overcome the particularly challenging barriers to the development of these drugs. IDSA agrees that it is important to ensure strong communication between FDA, CMS and any other agencies involved in incentivizing antibiotic R&D to ensure that companies are provided with consistent and predictable information regarding available antibiotic incentives.

As Congress continues its important work to provide additional incentives for antibiotic development, IDSA underscores the equally critical need to monitor the use of new and existing antibiotics, such as through the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN). Data on antibiotic use is critical to understanding and reducing the overuse of and misuse of these drugs, which puts patients at risk for adverse events and suboptimal outcomes and fuels the development of resistance. Usage monitoring is important for all antibiotics, and particularly for ADAPT or limited population antibiotics and antibiotics that receive increased reimbursement to protect patients and to protect the federal investment in these drugs by maintaining their utility. One way to increase data reporting on antibiotic use would be to connect reporting with increased reimbursement for certain antibiotics. This approach is similar to those used in other CMS programs.

Due to the different functions and legal authorities of the FDA, CMS, and CDC, Congress may opt to tailor antibiotic incentives to best achieve the ultimate goals of improving patient outcomes and saving lives. Thus, while the definitions and programs may differ, ultimately, the goal is streamlined coordination between all Federal health programs (including approval to reimbursement) to ensure that urgently needed new antibiotics are available and appropriately utilized.