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Testimony of
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Energy and Commerce Committee
Subcommittee on Health

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

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Introduction

Good morning and thank you to the Chairman and Members of the Committee for inviting me to testify today. I am the Chief Executive Officer of Achaogen, a company focused on the discovery, development and commercialization of novel antibiotics for treating infections caused by multidrug-resistant Gram-negative bacteria. Achaogen is a member of the Antimicrobial Innovation Alliance, a coalition created to address the unique challenges facing the research, development, and approval of new antimicrobial products, as well as their market viability, and includes Actavis-Forest Labs, AstraZeneca, Astellas, GlaxoSmithKline, Johnson & Johnson, Merck, Tetraphase and The Medicines Company.

This Committee's work through the GAIN Act has already made a significant impact and, initiatives, such as the 21st Century Cures, represent an important step towards addressing the paucity of new antibiotics for serious infections. I appreciate the opportunity to highlight the areas where we believe Congress has an opportunity to make a major difference.

Antibacterial resistance is one of the most significant medical challenges our country faces today. The rise and spread of bacteria that are resistant to multiple classes of antibiotics often leaves physicians with few to no options for treating patients with severe, life-threatening infections. A recent report from the CDC highlights that up to 50% of patients who contract bloodstream infections caused by pathogens known as carbapenem-resistant Enterobacteriaceae, or CRE, die from their infections.

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By way of background, I practiced as a physician for 10 years in the United Kingdom before moving to the United States to join Genentech, a California biotech company, where I spent 16 years and held multiple leadership positions spanning from early research to late stage clinical development. I was responsible for all stages of clinical development for products in all therapeutic areas outside of oncology. After Roche acquired Genentech, I was appointed as Senior Vice President of product development in the Asia Pacific region, based out of Shanghai, China. I joined Achaogen nearly four years ago to help address the challenge of antibacterial resistance.

Achaogen is a small business with fewer than 50 full time employees, and is based in South San Francisco, CA. Our lead product candidate, plazomicin, is currently being evaluated in a phase 3 clinical trial focused on CRE. These bacteria are resistant to carbapenem antibiotics, which are often considered to be our last line of defense in settings where other antibiotics are no longer active. Our phase 3 trial utilizes a "superiority" design intended to demonstrate a reduced number of deaths among patients treated with plazomicin-based therapy as compared to the best available antibiotic care. We have also developed a diagnostic assay that is being used in the phase 3 trial to measure plazomicin blood levels to optimize dosing on an individual patient basis.

The innovative trial design and the incorporation of the diagnostic assay required close consultation and coordination with both the drug (CDER) and diagnostic (CDRH) branches of FDA. The trial design was agreed upon through the Special Protocol Assessment, or SPA, process, which is intended to provide assurance to sponsors that the trial design will be sufficient for market approval of the drug. Plazomicin also was granted Fast Track Designation, allowing frequent interaction with the agency throughout the planning process. We found our interaction with the FDA to be extremely collaborative and believe this serves as a model for how the FDA can facilitate development of antibiotics in a setting of urgent unmet medical need.

The plazomicin program received the first contract awarded through the Broad Spectrum Antimicrobials program by the Biomedical Advanced Research and Development Authority (BARDA). The contract is designed to advance plazomicin through licensure by the FDA, and if fully realized, the contract will provide over $100 million in total funding. Achaogen maintains an active and productive research discovery team that is working on the next generation of antibiotic candidates for treating Gram-negative infections. We have previously received funding from the National Institute of Allergy and Infectious Diseases, or NIAID, and the Department of Defense for several of our research and development programs.

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My experiences at both large and small companies gives me insight into the way companies make decisions to invest in research and development programs and I appreciate the opportunity to share some of these today. The following are specific recommendations for actions this committee and others within the government can take to incentivize companies to discover, develop and commercialize the next generation of advanced antibiotics.

Reimbursement Reform and Other Economic Incentives

Compared to other therapeutic areas the economics of developing new antibiotics is not currently attractive to the pharmaceutical industry, resulting in many companies exiting from the antibiotic business. This has led to a decline in the number of new antibiotic approvals and has heralded the increase in antibiotic resistance. The commercial returns for an antibiotic are limited by the following factors:

1. Generic antibiotics are largely effective, given for short courses of therapy, and priced very cheaply (dollars per day);
2. Adoption of new antibiotics is slow as their use is restricted for the sickest patients, in order to preserve their useful life;
3. Reimbursement and use of higher priced new products is limited, particularly in the hospital setting where reimbursement for the antibiotic is typically obtained through a fixed payment that is intended to cover the total cost of patient care;
4. Longer-term commercial returns are eroded by the unavoidable development of bacterial resistance to new antibiotics over time.

As pharmaceutical companies prioritize their R&D efforts based on metrics such as Return on Investment (ROI) or Net Present Value (NPV), antibiotics lose out to other more commercially favorable therapeutic areas such as diabetes, cardiology, and oncology, where resistance development is not a concern and where new drugs are taken for prolonged periods and priced more in line with the value provided. Antibiotics are truly life-saving medicines that can give a patient back years of life, yet a typical branded antibiotic may command only $3,000/course of therapy. In stark contrast, branded oncology agents, which may only provide only months to a few years of extra life, typically are priced between $40,00-$70,000 for a course of therapy.

A number of incentives have been proposed or implemented to help promote antibiotic development. The GAIN Act provides for priority review and an extra 5 years of data exclusivity for qualifying products. However, these benefits are modest and additional incentives are urgently needed in order to significantly improve the economics and spur development. The DISARM Act (Developing an Innovative Strategy for Antimicrobial

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Resistant Microorganisms), sponsored by Congressmen Peter Roskam and Danny Davis and supported by many of you, has been proposed as a way to address the pricing challenges faced by new antibiotics. This legislation would reform reimbursement of qualifying antimicrobial products in the hospital setting, allowing value-based pricing. This would provide a powerful incentive, as today the pricing of new antibiotics used in the inpatient setting is limited by fixed reimbursement based on the patient's diagnosis group (e.g., MS DRG, Medicare Severity Diagnosis-Related Group). Currently, the payment to the hospital is the same regardless of the price of the antibiotic used, so hospitals are incentivized to use the cheapest, but not always the most effective, antibiotic. By providing separate reimbursement for qualifying antibiotics, the DISARM Act would help to minimize incentives to choose the cheapest antibiotics and provide manufacturers with the opportunity to price new antibiotics in a way that is commensurate with the value provided. Moreover, the DISARM Act would equalize the payment system for outpatient and inpatient product use, so manufacturers would be less inclined to focus on less serious pathogens and infections simply because of pricing advantages in the outpatient setting.

Achaogen supports passage of the DISARM Act and would like to see reimbursement for qualifying antibiotics extended beyond Medicaid and Medicare patients to patients covered by private insurance. In the latter case, private insurance would be supplemented with a government payment to the hospital for the antibiotic.

Given the urgency of the antibiotic resistance problem, we also believe additional incentives are needed to ensure we have a robust pipeline of new antibacterial agents. Such incentives could include tax credits, payments for the completion of key development milestones (e.g., completion of Phase 1, Phase 2, Phase 3, Approval, etc.), and government subsidies should drug sales fall below certain minimums.

FDA Approval Pathways Based on Limited Populations

Achaogen also supports passage of the ADAPT (Antibiotic Development to Advance Patient Treatment) Act and the establishment of new regulatory approval pathways for antibiotics that target specific and limited patient populations with high unmet medical need. The ADAPT Act will provide FDA with increased flexibility, beyond what is currently available, to promptly approve those agents intended to treat serious and life-threatening infections based on evidence that may come from clinical datasets of limited size, supplemented by pharmacologic or pathophysiologic data and phase 2-type studies.

Traditionally, antibacterial agents have been studied in large patient populations enrolled in non-inferiority clinical trials that focus on one site of infection (e.g., pneumonia, intra-abdominal

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infection). More recently, regulatory initiatives in both the US and Europe have resulted in new guidance describing streamlined development programs and clinical trial designs for drugs to treat serious bacterial diseases in patients with unmet medical need. The development program for plazomicin has been adapted to become one of the FDA examples of a streamlined program: a single Phase 3 randomized active-controlled superiority study to determine the efficacy and safety of plazomicin in the treatment of CRE infections. However, due to the need to power the study to demonstrate statistical significance for a mortality endpoint and the relative rarity of these infection types, the enrolment period for this study is expected to be 3 years. In contrast, in Europe a corresponding EMA guidance extends more flexibility in the same scenario of unmet clinical need and does not require inferential statistical testing.

The ADAPT Act should authorize FDA to place greater reliance on pharmacokinetic/pharmacodynamic (PK/PD) determinations based on animal and in vitro models (supplemented with clinical PK/PD data as appropriate). ADAPT should also mandate that FDA revisit, within a reasonable time frame, breakpoints of marketed drugs in the same class as a newly approved drug, to ensure consistency within the class.

ADAPT is important to manufacturers of antibiotics designed specifically to treat multidrug resistant (MDR) infections because it provides an alternative regulatory mechanism that allows for more rapid access to patients based on limited data in that population. It also provides the manufacturer flexibility in further product development, either by the continuation of restricted use or label expansion based on further clinical evidence.

In order for new drugs to be available ahead of the emergence of unacceptably large numbers of drug resistant infections, Congress must enact legislation that authorizes the FDA to approve new antibiotics for limited patient populations based on limited clinical trial data but where the totality of the available scientific and clinical evidence supports the benefit/risk profile for the antibiotic, while acknowledging and reflecting the greater uncertainty associated with limited clinical testing in the product label.

Development and Use of Diagnostic Tests

When faced with a patient who has a serious bacterial infection, physicians need to make rapid antibiotic treatment decisions, as a delay in administration of an effective antibiotic by just one hour significantly increases patient mortality. Existing traditional bacterial identification and antibiotic susceptibility tests may take up to 72 hours to complete, so broad-spectrum antibiotics, intended to cover a variety of pathogens, are administered empirically before the bacterial species and antibiotic susceptibility are known. Rapid diagnostic tests are evolving and are

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intended to identify the species of bacteria causing the infection and, with some tests, potential resistance to different antibiotics in a much shorter timeframe. . In an ideal world, rapid diagnostic testing would allow bacterial identification and antibiotic susceptibility to be determined at the point of patient care to enable healthcare professionals to decide on the most appropriate antibiotic as quickly as possible. Diagnostic tests can also be used to monitor drug exposure (patient blood levels) to individualize dosing for each patient, which has been shown to improve outcomes. We believe the federal government should be providing significant support and incentives to companies and innovators of rapid and cost-effective diagnostics that will advance antibiotic stewardship and clinical care.

There is an opportunity to significantly streamline the regulatory process for development and approval of companion diagnostic tests. Currently, the FDA expects that the therapeutic product sponsor will address the need for an approved or cleared companion diagnostic device in its therapeutic product development plan, or will develop its own companion diagnostic device. We contend that the current regulatory model of approving one diagnostic, on a single platform, for one drug is not scalable and risks creating an unnecessary barrier to patient care and antibiotic stewardship. In the rapidly evolving field of diagnostic devices it is difficult to predict which test will be most appropriate at the time of product launch. Furthermore, one size does not fit all microbiology laboratories. Laboratories need the flexibility to run the tests that are most suitable for the equipment, expertise and workflow within their laboratory.

During the conduct of trials involving drugs and diagnostics, sponsors and the FDA need to be able to work flexibly with laboratories closest to the point of care, and to be able to use a variety of tests that facilitate enrollment of patients with rare multi-drug resistant infections. There is a need for an expedited approach to diagnostic development to keep pace with the changes in technology. We need regulations that support a more flexible approach under a risk-based assessment that considers at its core, the overall benefit risk for patients. The regulations should provide the FDA with the flexibility to customize the required analytical studies for each assay at the time of NDA filing, as well as the data and testing related to quality systems, manufacturing, software testing and documentation, so that they support the safe and effective use of the drug.

Sustained Funding for Antibiotic Research and Development

Finally, it is crucial to secure a long-term commitment to funding for antibacterial research and development. Less than a decade after the first antibiotics, sulfonamides and penicillin, were introduced in the 1930s and 1940s, bacterial strains resistant to these antibiotics were discovered. Indeed, resistance has eventually developed to every antibiotic that has been used in the clinic.

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Thus, we need to maintain a robust pipeline of antibiotics so that effective therapies always remain available to patients. The funding that Achaogen has received from BARDA, NIAID, and the DOD illustrates how public-private partnerships can successfully advance antibacterial research and development.

The investment from BARDA in the plazomicin program has supported the design, initiation, and ongoing performance of our phase 3 superiority trial, the development of the plazomicin diagnostic assay, plus advances in the plazomicin manufacturing process. The funding from BARDA came at a time when we were completing a phase 2 clinical trial of plazomicin under an investment from the Wellcome Trust, and it enabled Achaogen to advance plazomicin to the next stage of development. We support increased funding for the Broad Spectrum Antimicrobial program, and the expansion of BARDA's mission to allow investment in programs designed to address the public health threat posed by antibacterial resistance in addition to their current work to combat biodefense threat pathogens.

The role that BARDA has in advancing novel antibiotics through late stage development will be bolstered by the recent launch of the Antimicrobial Resistance Leadership Group, or ARLG, through support from the National Institute of Allergy and Infectious Diseases, or NIAID, an Institute within the National Institutes of Health. The goal of this group is to streamline the development of novel antibiotics by providing an existing network of clinical sites to more rapidly enroll patients in clinical trials, and by standardizing clinical trial designs through the development of master protocols. We support the continued funding of the ARLG and other initiatives to develop clinical trial networks that will streamline operational aspects of performing antibiotic clinical trials.

It is also important to ensure steady funding for early stage efforts to discover the next generation of antibacterial candidates, in order to maintain a sustained pipeline of effective antibiotics. The NIH historically has supported this stage of development, and indeed, Achaogen has received funding from NIAID. We support continued funding of early antibiotic R&D through specific NIAID funding devoted to antibacterial discovery and early development.

The process from initiation of an antibiotic discovery program through clinical trials and licensure can take well over 10 years. Given this long timeline, it is important to provide incentives to launch antibacterial research programs on an ongoing and predictable basis. Congress must develop a long term strategy for funding antibiotic research and development that is sustainable as a benefit to public health. The funding for BARDA and NIH must be guaranteed and ring-fenced from diversion for other purposes, in order to assure antibiotic discoverers of continued support for their efforts.

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Conclusion

We propose a multifaceted approach to incentivize companies to develop new antibiotics that is based upon the following four points:

1. Passage of the DISARM Act and consideration of other incentives such as tax credits and milestone payments
2. Passage of the ADAPT Act and consideration of approval pathways based on limited clinical data sets and novel endpoints
3. Streamlined approval pathways for rapid diagnostic assays that enable selection of appropriate antibacterial therapy, in order to prevent delays in approval of antibiotics where there is a high unmet need
4. Increased, sustained, and dedicated funding to support antibacterial research from early discovery through late stage clinical development, specifically to include funding for BARDA and NIH/NIAID

Together, the initiatives would provide additional incentives for companies to invest in and sustain antibacterial research and development that will be needed to maintain a robust pipeline of life-saving antibiotics. We believe that Congress must take aggressive action now to prevent the public health threat from multi-drug resistant bacterial infections from growing beyond current levels.