Written Testimony
House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations

"Combatting Superbugs: U.S. Public Health Responses to Antibiotic Resistance"

Statement of

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Good morning, Chairman Murphy, Ranking Member DeGette, and Members of the Committee. Thank you for the opportunity to testify before you today about our government's efforts to combat antimicrobial-resistant bacteria. I am Dr. Richard Hatchett and I serve as the Acting Director of the Biomedical Advanced Research and Development Authority (BARDA), a component of the Office of the Assistant Secretary for Preparedness and Response (ASPR) in the U.S. Department of Health and Human Services (HHS). In this capacity, I also serve as the Acting Deputy Assistant Secretary for Preparedness and Response.

BARDA was established by the Pandemic and All-Hazards Preparedness Act (PAHPA) in December 2006 to support the advanced research, development and procurement of novel and innovative medical countermeasures such as vaccines, antimicrobial drugs, and medical devices (including diagnostics) to address the medical consequences of chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring and emerging threats, such as the 2009-H1N1 influenza, H7N9 influenza, Ebola, and Zika viruses. Through the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), ASPR is working on efforts to address the growing threat of antimicrobial resistance, which has expanded in recent years. I appreciate the opportunity to highlight our progress to-date and underscore the significant challenges remaining.

BARDA works with our HHS and other federal agency PHEMCE partners to transition medical countermeasures from early development into advanced development and ultimately to an application for Food and Drug Administration (FDA) regulatory review and approval. Advanced development includes critical steps needed for a product to be ready for use. This involves

optimizing manufacturing processes so products can be made in quantity to scale, creating and optimizing assays to assure product integrity, conducting late-stage clinical safety and efficacy studies, and carrying out pivotal animal efficacy studies that are often required for approval. Since 2006, BARDA has managed the advanced development of nearly 150 medical countermeasures for CBRN threats and pandemic influenza. Six of these products have received FDA approval in the last two years alone.

Today, we face a growing threat that has the potential to impact more Americans than an infectious disease outbreak or terrorist attack with a biological agent. Antibiotics and other antimicrobial agents have been effective in treating common infections since their widespread use in the 1940s. They are essential to the practice of modern medicine. The problem of antimicrobial resistance was recognized shortly after the first antibiotics, the sulfonamides, were introduced in the late 1930s, and has always presented concerns. Historically, when an infection demonstrated resistance to one class of antibiotics, clinicians would simply switch to a different class. However, the past two decades have witnessed a significant increase in the spread of organisms resistant to multiple classes of antibiotics. Compounding the problem, the pace of introductions of new antibiotics has slowed considerably largely because there is not a sufficient private sector incentive to invest in antibiotic development.

Gram negative bacteria, in particular, have become increasingly resistant to available antimicrobial drugs, and deadly and extremely difficult-to-treat pathogens such as carbapenem-resistant Enterobacteriaceae (CRE) have become more widespread. Colistin, which has long been considered a drug of last resort due to its serious side effects, is being used increasingly to

treat infections with such bacteria. The recent emergence of a plasmid-borne colistin resistance gene, *mcr-1*, thus portends the emergence of truly pan-drug resistant bacteria, for which no current antibiotics are effective. The report three weeks ago of *mcr-1*-carrying *E. coli* in a patient with a urinary tract infection in Pennsylvania starkly highlights the urgent need for proactive action to combat antimicrobial resistance.

Along with our PHEMCE colleagues, BARDA has worked aggressively over the last six years to meet this threat and to re-engage academia and industry in the development of new antibiotics and antiviral drugs. Consistent with an ASPR strategic priority to invest in biodefense products and technologies, which also support everyday applications, BARDA's development of new antibiotics and antiviral drugs is critical to our defense from a naturally occurring threat or terrorist attack. It also has the potential for substantial day-to-day benefit for health care across the U.S. In 2010, BARDA established a Broad Spectrum Antimicrobial (BSA) program to support the development of new classes of antibiotics. Over time we have built out our portfolio and now manage a pipeline of nine products.

BARDA's objectives in establishing the BSA program were to: (1) revitalize the antibacterial pipeline through the support of public-private partnerships targeting novel unprecedented and precedented classes of antibiotics; (2) emphasize programs that address the immediate public health threat of multidrug resistant strains of hospital and community acquired pathogens; (3) provide a biodefense capability to bridge the response between the first clinical case of threat agent infection to when mass dispensing of medical countermeasures is initiated; and (4) enable

the evaluation of products for all biothreat pathogens via the development of animal models and tools to support regulatory approval.

We have achieved notable successes in this area. We have built a robust portfolio of broad spectrum antibiotics that possess activity against Gram negative bacteria, which is noteworthy given the limited number and increasing ineffectiveness of antibiotics against these deadly and difficult-to-treat bacteria. Five of our programs have reached Phase 3 clinical development, the last stage before an application for FDA approval, and two products have completed the pivotal registration clinical studies required for approval. One relationship, with Astra Zeneca, is noteworthy in that it reflects a groundbreaking effort to coordinate funding with the EU's Innovative Medicines Initiative (IMI) and thereby speed the development of Astra Zeneca's lead antibiotic, aztreonam/avibactam.

In 2014, the President's initiative on Combating Antibiotic-Resistant Bacteria (CARB) directed BARDA to "develop new and next-generation countermeasures that target antibiotic-resistant bacteria that present a serious or urgent threat to public health" through our advanced development of both drugs and diagnostics.

As outlined in the companion National Strategy and Action Plan for CARB, PHEMCE partners were given clear goals for addressing antimicrobial resistance, objectives for meeting those goals, and milestones to measure progress and success. ASPR, in cooperation with its federal partners, has been engaged in laying out a strategy to address the medical consequences of antimicrobial resistance. Within HHS, we are engaged in strategic advisory boards and working groups dedicated to addressing many of the requirements in the national action plan such as the

Interagency Task Force on Antimicrobial Resistance, the Transatlantic Taskforce on Antimicrobial Resistance, and the National Strategy for Research and Development working group.

The recent identification of an *mcr-1*-carrying *E. coli* bacteria in a patient with a urinary tract infection in Pennsylvania highlights the serious health threat posed by drug-resistant bacteria. The nine antibacterial products that BARDA is developing address a range of drug-resistant bacterial threats, including *E.coli*, that were identified as either urgent or serious by the CDC in their 2013 report on the public health crises of antibiotic-resistant infections. A number of these have shown promise for the treatment of infections due to carbapenem-resistant Enterobacteriaceae (CRE). A few of the drugs in BARDA's portfolio have already shown direct *in vitro* activity against bacteria harboring *mcr-1* (so-called "superbugs") and if approved these products could provide some relief from resistance concerns in the future. More broadly, each of the products in the BARDA portfolio is a broad spectrum antibiotic that possesses activity against Gram negative bacteria, which is important because comparatively few antibiotics active against Gram negative bacterial infections are in development and new drugs to treat such infections are desperately needed. BARDA is actively working with industry to pursue innovate approaches and strategies to improve our nation's arsenal against antibiotic resistant organisms.

Combating antibiotic resistance is a public health and national security priority, and BARDA has developed a number of innovative partnership models to support this goal. In recent years, BARDA has pioneered the use of portfolio partnerships, in which companies investigate the advancement of multiple drug candidates at the same time. Funding a portfolio of products,

rather than just a single candidate at a time increases the probability of bringing a successful drug to market. BARDA has established these partnerships using the PAHPA-granted Other Transaction Authority (OTA) to create flexible, cost-sharing business partnerships between the government and industry. Portfolio-based funding reduces risk by allowing for the reallocation of resources across activities and among drug candidates if technical or business risks materialize. Since 2013, BARDA has successfully used its OTA twice to establish public-private partnerships. The establishment of the partnership with Astra Zeneca fulfilled a requirement in the CARB National Action Plan to create at least one additional portfolio partnership with a pharmaceutical or biotechnology company by March 2016 to accelerate development of new antibacterial drugs, and several others are currently in negotiations.

BARDA works closely with other government funding agencies, specifically the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health, to provide support of product development from early stage discovery through to approval and procurement. While NIAID primarily supports early stage discovery of new drugs, vaccines, and diagnostics and preclinical product development up through Phase 1 clinical studies, programs normally become eligible for BARDA funding once an application to administer an investigational drug to humans is filed with FDA and the project is in Phase 1 development or later. BARDA works closely with our interagency partners, including NIAID and the programs in the Department of Defense, to identify and transition projects within their portfolios to BARDA where we can support the later stage clinical development of products from Phase 1 to approval.

In today's marketplace, innovation often occurs in small biotechnology companies and in academic laboratories that lack the resources and expertise to move candidates along the development path from lead optimization to clinical development. Many promising early stage candidates, without the appropriate resources and support, will be unable to advance to late stage clinical development and approval. To overcome this problem, BARDA and NIAID are working together to establish and operationalize a new initiative we are calling the CARB Accelerator. The CARB Accelerator will serve as an incubator for new products and explicitly seeks to reinvigorate the early stage antibiotic pipeline and repopulate the late stage clinical development pipeline with new and promising antibiotics. The CARB Accelerator will fund research and development activities to help progress candidate products from the proof-of-concept stage through pre-clinical development. BARDA will provide direct funding to launch the Accelerator in 2016, with a goal to support the program thereafter for five years, while NIAID will provide access to an array of product development support services. NIAID and BARDA will collaborate in managing the program and its investments through a joint oversight committee. BARDA's goal for the Accelerator is to stimulate the early stage development of new antibiotic candidate products and to progress products to the step of filing an FDA Investigational New Drug (IND) application, which is required before drugs can enter human clinical trials. After receiving the FDA's authorization, products can then enter into the clinical development phase and thus become eligible for direct BARDA support. Successful products will emerge from the Accelerator as graduates with resources, networks and a robust product development strategy to support further clinical development.

In 2016, the Accelerator will accept proposals from innovators seeking support for the nonclinical development of their candidate products. BARDA looks forward to engaging the community of researchers and product developers through another novel public private partnership and re-inventing how government is able to partner with industry to address the urgent problem of antimicrobial resistance.

As new forms of antibiotic resistance continue to spread worldwide, the prospect of bacterial strains resistant to all available antibiotics can no longer be ignored; the continued development of new options for treating drug-resistant bacteria will be essential to preserving our ability to effectively combat infections. ASPR and its partners will continue to play a critical role in leading the charge against these threats, both present and future. We look forward to working with Congress to develop new antimicrobial therapies and non-traditional approaches to address the global challenge of antimicrobial resistance. Thank you again and I look forward to your questions.