Written Testimony
House Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education, and Related Agencies

"The Ebola Epidemic: The Biomedical Advanced Research and Development Authority's Response"

Statement of

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Good morning, Chairman Cole, Ranking Member DeLauro, and distinguished Members of the Subcommittee. Thank you for the opportunity to speak with you today and for your generous support and funding in our Ebola response efforts. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary for Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS), as well as a former vaccine developer in industry.

ASPR is supporting the federal government's Ebola response effort through policy development, advancements in medical countermeasures (MCM), logistical support for deployed personnel, and broader community and health care preparedness and resilience through grant funding, dissemination of information to state and local partners, and communication with international partners concerning health security issues. Originally authorized by the Pandemic and All-Hazards Preparedness Act (PAHPA) in 2006 and then reauthorized in 2013, ASPR leads the nation in preparing and responding to -- and recovering from – public health and medical disasters and emergencies.

BARDA is the federal government agency, within ASPR, created in 2006 by PAHPA to support advanced research and development and the procurement of novel and innovative medical countermeasures (MCMs). These MCMs: vaccines, therapeutics, antiviral and antimicrobial drugs, diagnostics, and medical devices, address the needs of the entire nation to mitigate the medical consequences of man-made chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring and emerging threats like the 2009 H1N1 pandemic, the 2013 H7N9 influenza outbreak, and the current Ebola epidemic.

Medical countermeasure development is risky, lengthy, and costly, with many inexperienced developers failing and many larger pharmaceutical companies avoiding the sector

completely. BARDA serves as a bridge over a critical gap referred to as the "Valley of Death" in MCM development. BARDA transitions candidate-products from early development into advanced development and towards potential Food and Drug Administration (FDA) approval and then stockpile procurement, through direct support, public-private partnerships, and technical core service assistance programs.

Advanced development includes critical steps needed to transform a candidate to a product that is ready to use. These steps include optimizing and validating manufacturing processes such that products can be made at commercial scale; optimizing product formulation for optimum field usage, storage, and product longevity and effectiveness; 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 regulatory approval.

Since 2006, BARDA has funded and successfully managed the advanced development of more than 160 MCMs for CBRN threats and pandemic influenza. Twenty-one BARDA-supported products have been approved by the FDA with nine since 2012. BARDA has made twelve of these MCMs available for use under Project BioShield and maintains the national pre-pandemic influenza vaccine stockpile for H5N1 and H7N9 influenza viruses that has the potential to protect tens of millions of persons.

Designed to save cost and time in product development and manufacturing, BARDA established core service assistance programs to assist medical countermeasure product developers on a daily basis while ensuring rapid and nimble response in a public health emergency. These four programs– the Nonclinical Studies Network (NCSN), the Centers for Innovation in Advanced Development and Manufacturing (CIADM), Fill Finish Manufacturing

Network (FFMN), and the Clinical Studies Network (CSN) - augment technical and regulatory assistance provided directly by BARDA. These investments in establishing a National Medical Countermeasure (MCM) Response Infrastructure are playing a major role in the Nation's response to the current Ebola epidemic and will become even more vital for MCM responses to public health and national security emergencies in the coming years.Over the last decade, the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) supported basic research and early-stage development of numerous Ebola and Marburg virus MCM candidates. Last summer, BARDA prepared and implemented a new rapid response Ebola MCM strategy for the development, manufacturing, and nonclinical and clinical evaluation of Ebola therapeutics and vaccines. Subsequently, BARDA reached deep into the Ebola MCM early development pipeline and transitioned multiple vaccine and therapeutic candidates into advanced development, ensuring clinical trials and large scale manufacturing to implement this strategy.

Strategy, Implementation, & Results

BARDA's Ebola MCM strategy for development, manufacturing, and evaluation of monoclonal antibody and antiviral drug therapeutic candidates outlines three goals: make clinical trial materials with industry partners, ensure safety and efficacy evaluation in animal or clinical studies, and support improved product manufacturing.

First, BARDA re-prioritized program activities in FY 2014 to provide funding and extensive technical assistance for the development and scaled-up manufacturing of the ZMapp monoclonal antibodies, the most promising Ebola therapeutic candidate in the pipeline, albeit using an unproven biotechnology, tobacco plants, that the National Institute of Allergy and Infectious Diseases (NIAID), the Department of Defense's Defense Threat Reduction Agency ,

and Public Health Agency of Canada had supported in early development. ZMapp was provided in 2014 to eight Ebola patients under compassionate use and emergency Investigational New Drug applications. ZMapp continues to be produced in Kentucky for clinical safety and efficacy studies. NIAID's clinical studies are on-going now in West Africa for evaluation of ZMapp. Further, production yields for ZMapp have been improved at least two-fold with BARDA subject matter experts serving as in-plant advisors throughout the manufacturing process.

Next, when it was determined that the production capabilities of ZMapp would be insufficient from one manufacturer alone, BARDA engaged other tobacco biopharmaceutical companies to make ZMapp using their own tobacco plants, expression systems, and facilities to produce more antibody product. In FY 2015, Medicago and Fraunhofer began to produce ZMapp using their own tobacco plants, expression systems, and facilities. These ZMapp counterparts are now being evaluated in animal challenge studies against ZMapp using the BARDA National MCM Response Infrastructure to ensure prioritized testing can be achieved. Increased production capacity was realized using these alternative production processes, making more ZMapp available.

BARDA executed the third element of the Ebola MCM strategy by partnering with large pharmaceutical companies that specialize in the development and production of commercial monoclonal antibodies for other diseases; the purpose of the partnership is to develop Ebola monoclonal antibodies using specialized Chinese Hamster Ovary (CHO) cells, and thereby to provide additional therapeutic candidates. This approach would also provide a readily available commercial-scale manufacturing process and facilities necessary to produce large qualities of antibodies. BARDA partnered with Genentech and Regeneron to develop in record time new forms of ZMapp and brand new Ebola monoclonal antibody therapeutic candidates using state-

of-the art monoclonal antibody technologies and specialized CHO mammalian cells capable of immediate commercial scale production. Preliminary results in nonhuman primate challenge studies showed that the Ebola monoclonal antibodies produced in these CHO cells protect Ebola-infected animals as well as does ZMapp and thus afford another set of therapeutic candidates for clinical evaluation.

The fourth therapeutic element of the strategy would have BARDA invest in the advanced development of Ebola antiviral drug candidates once promising results from nonhuman primate challenge studies and Phase1 clinical studies became available. BARDA transitioned a new Ebola antiviral drug candidate, BioCryst's BCX4430, from early development at NIAID to advanced development. Clinical lots of this drug candidate are being manufactured for possible clinical efficacy trials in West Africa.

With FY 2015 Ebola funds, we have expanded our portfolio of Ebola therapeutic candidates and increased the production capacity to produce larger quantities of Ebola monoclonal antibodies and a new antiviral drug.

Similarly, BARDA's strategy for Ebola vaccines focused on the development, manufacturing, and clinical evaluation of multiple vaccine candidates with federal and industry partners. There are four goals: make clinical investigational lots of vaccine for clinical trials as soon as possible; support the clinical trials with technical expertise and infrastructure; improve vaccine manufacturing processes for greater product yield and commercial-scale manufacturing capability; and, the development of more thermostable vaccines for easier and longer storage.

With FY 2015 Ebola funds, BARDA supported the development, manufacturing, and evaluation of three Ebola vaccine candidates from several companies—Newlink Genetics/Merck,

GlaxoSmithKline, and Profectus. Additional vaccine candidates are also under active consideration.

BARDA's funding and technical support are enabling progress towards clinical lot production, commercial-scale vaccine production for potential mass vaccination campaigns, and the development of more thermostable formulations for easier storage and use.

With the new vaccine candidates, BARDA's portfolio of Ebola medical countermeasures has grown from no candidates in early 2014 to ten vaccine and therapeutic candidates in eight months to address the current and future Ebola epidemics and potential Ebola-related bioterrorism acts.

Ebola response results included the transformation of BARDA's core service assistance programs into a National MCM Response Infrastructure that provided rapid response and assistance to NIAID, CDC, and industry partners in the current Ebola epidemic and may assist in future public health emergencies. This infrastructure expedited the development and manufacturing of multiple investigational Ebola therapeutics and vaccines. For example, BARDA's National MCM Response Infrastructure , which began in 2010 with 17 laboratories, conducted key animal challenge studies on several promising investigational Ebola monoclonal and small molecule therapeutic candidates that enabled them for further consideration. Established in 2012, BARDA's CIADMs have worked to expand the production of new Ebola monoclonal antibodies using CHO cells. In 2013, BARDA established the FFMN as a pandemic influenza preparedness measure that has been used to formulate and fill multiple Ebola antibody and vaccine candidates into vials for on-going clinical efficacy studies in West Africa. BARDA has provided both BARDA clinical and engineering staff and two members of our CSN, created in 2014 to aid MCM developers with clinical research, to help CDC conduct Ebola vaccine

clinical trials in Sierra Leone. BARDA's modeling hub has coordinated federal and international modeling efforts for Ebola epidemiology and interventions as domestic and international scenarios and capabilities evolved. The investments that we have made since 2010 to create this infrastructure are playing a major role in the nation's response to the current Ebola epidemic and will be there with MCMs for future public health emergencies.

BARDA, along with our PHEMCE partners, has successfully used existing and new public-private partnerships with industry and academia to ensure that we have the best MCMs to protect the national health security of the United States in emergencies. Over the past five years, BARDA—with NIH, CDC, FDA, and industry partners— has built a flexible and rapidly-responsive infrastructure to develop and manufacture MCMs. In 2013 in response to the H7N9 influenza outbreaks in China, the BARDA and PHEMCE partners mobilized these partnerships to design, develop, manufacture, clinically evaluate, and stockpile several vaccine candidates in record time. In the current Ebola response, BARDA once again called upon existing partners and made new partnerships with a wider array of partners that included other countries, specifically Canada and the affected and at-risk African countries; the World Health Organization; the Bill and Melinda Gates Foundation; and others. These expanded partnerships have been critical to our efforts to address the current Ebola epidemic.

Going forward BARDA will continue implementing and adapting the Ebola MCM strategy to demonstrate whether these and next generation Ebola therapeutic and vaccine candidates are safe and efficacious. Improvements to Ebola manufacturing to ensure robust and controlled manufacturing at commercial scale will be pursued to ensure mass vaccination and widespread therapeutic usage are feasible. Better formulations of Ebola therapeutics and vaccines for field usage and storage will be developed. Multivalent vaccines effective for

prevention of Ebola and other viral hemorrhagic viruses will be developed to address future epidemics and will be stockpiled against potential bioterrorism acts with these viruses. Teaming with NIAID and CDC, BARDA will invest in research and clinical infrastructure in West Africa and elsewhere to have readily available relationships and networks to test rapidly new MCMs for emerging infectious diseases. BARDA will support development of next generation rapid diagnostics for Ebola and other pathogens. Lastly BARDA will formalize and expand the capabilities of our national MCM response infrastructure with innovative technologies that afford rapid and nimble response to meet the challenges of future known and unknown emerging infectious diseases.

Conclusion

BARDA with our federal and industry partners has responded rapidly and successfully with the development of new and innovative Ebola MCMs in record time during this Ebola epidemic, as these MCM candidates are now undergoing critical clinical evaluation. Yet there is much more to do to bring this epidemic down to zero, to identify and implement lessons learned, and become better prepared proactively for the next Ebola outbreak, bioterrorism act, influenza pandemic, or emerging infectious disease that appears on our door steps. The investments in Ebola MCMs and response have addressed much of the current epidemic, but additional funding will be needed to finish this mission and prepare ourselves for the next one.

Again, I would like to thank this Subcommittee for its generous and continued support and for the opportunity to testify. I look forward to your questions.