



**Written Testimony  
Committee on Energy and Commerce  
Subcommittee on Oversight and  
Investigations  
United States House of Representatives**

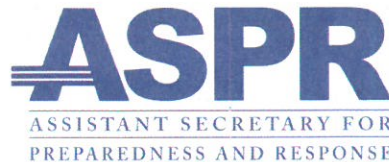
**“Seasonal and Pandemic Influenza  
Preparedness: The Biomedical Advanced  
Research and Development Authority’s  
Response”**

*Statement of*

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**For Release on Delivery  
Expected at 10:00 AM  
Tuesday, February 3, 2015**

Good morning, Chairman Murphy, Ranking Member DeGette, and distinguished Members of the Subcommittee. Thank you for the opportunity to speak with you today about our Government's seasonal and pandemic preparedness and response medical countermeasure (MCM) efforts and challenges. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary to the Assistant Secretary for Preparedness and Response (ASPR) of the Department of Health and Human Services (HHS).

BARDA is the Federal Government Agency mandated to support advanced research and development and procurement of novel and innovative MCMs such as vaccines, therapeutics, antiviral and antimicrobial drugs, diagnostics, and medical devices for the entire Nation to address the medical consequences of man-made chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring and emerging threats like the H1N1 pandemic, last year's H7N9 influenza outbreak, and the current Ebola epidemic.

By supporting advanced research and development of MCM candidates, BARDA addresses the medical consequences of these threats and bridges the gap between early research and development and Food and Drug Administration (FDA) approval and potential procurement of MCMs for novel threats. 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 formulations, storage, and product longevity and effectiveness; creating, optimizing, and validating 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 of

CBRN MCMs. Since 2006, BARDA has funded and successfully managed the advanced development of more than 150 MCMs for CBRN threats and pandemic influenza. Eight of these products have received FDA approval in the last two years alone, and twelve of these products have been made available for use under Project BioShield. BARDA has supported the development of 18 influenza medical countermeasures since 2007 that were used in the 2009 H1N1 pandemic and stockpiled for avian influenza H5N1 and H7N9 outbreaks.

Seasonal influenza occurs every year. Periodically, however, novel influenza virus strains for which there is little human immunity emerge and these can cause global pandemics like the H1N1 2009 pandemic, or worse the pandemic of 1918. Because influenza viruses mutate as they traffic and reassort among birds, swine, and man primarily, achieving protection against seasonal influenza viruses is a significant challenge. Means to control and address the medical and public health consequences of influenza include social distancing, proper hygiene practices, vaccination, antiviral drugs, and diagnostics. In the last decade we have been reminded how complex management of seasonal and pandemic influenza are both globally and nationally. These reminders have included the following:

- the reemergence of H5N1 avian influenza in 2003 in Vietnam with high mortality in humans and spread from Southeast Asia to the Middle East through 2009,
- the shutdown of one of the two major influenza vaccine suppliers to the U.S. in 2004-2005,
- the rapid emergence of drug resistant H1N1 mutants to influenza neuraminidase inhibitors in 2008-2009,
- the H1N1 pandemic of 2009-2010,

- the emergence of seasonal H3N2 virus variants in 2012 in the Midwest primarily affecting children,
- the emergence of H7N9 avian influenza viruses in China in 2013 that were highly virulent for humans, and
- the mismatches of seasonal influenza vaccines with circulating H3N2 viruses in 2012-2013 and again this year.

The potential of the H5N1 virus to become a severe influenza pandemic resembling the 1918 pandemic led to the issuance and implementation of the *National Strategy for Pandemic Influenza* (2005) and sparked important efforts to develop new influenza medical countermeasures, establish vaccine and antiviral drug stockpiles, and expand domestic vaccine manufacturing. The lessons learned from the H1N1 pandemic resulted in the President's Council of Advisors on Science and Technology's (PCAST) *Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* (2010) recommending improvements in virus surveillance, vaccine research and development, and influenza vaccine manufacturing. HHS reexamined and implemented revised plans to develop new influenza vaccines, antiviral drugs, and diagnostics; to assess the size, composition, and usage of influenza vaccine and antiviral drug stockpiles, and to expand our domestic influenza vaccine manufacturing infrastructure and capacity. The common thread throughout these preparedness and response plans is that seasonal and pandemic influenza are inextricably interwoven; what we do in one area directly affects what we do in the other.

For influenza vaccines, HHS set as a goal “more and better influenza vaccines sooner” meaning that we need more effective vaccines available in large quantities for seasonal and pandemic influenza faster. For influenza antiviral drugs, we looked for new drugs focused on new viral and host targets less vulnerable to drug resistance and that would be effective against severe hospitalized cases of influenza. For influenza diagnostics, we supported development of more rapid and sensitive diagnostics for point-of-care clinical settings and high throughput diagnostics for State, national, and commercial laboratories to increase capacity, sensitivity, and rapidity.

HHS, as integrated and coordinated Federal Agencies – NIH, CDC, FDA, ASPR, ASH, and BARDA- has partnered with industry and academia to address these seasonal and pandemic influenza challenges. ASPR coordinates overall HHS and government-wide influenza pandemic preparedness and response strategies and action plans in concert with the seasonal influenza activities managed out of the National Vaccine Program Office in the Assistant Secretary for Health. BARDA is directly responsible for working with industry and Federal partners to:

(i) support advanced development of new influenza vaccines, antiviral drugs, and diagnostic devices leading to FDA approval for the U.S. market; (ii) improve influenza vaccine manufacturing resulting in greater vaccine production yields and availability sooner; (iii) build and maintain stockpiles of pre-pandemic influenza vaccines for the critical workforce and antiviral drugs at the Federal and State levels; and (iv) expand domestic and global pandemic influenza vaccine manufacturing infrastructure and capacity multifold.

BARDA’s pandemic influenza mission is not yet completed. Although the recent introduction of quadrivalent and high-dose seasonal influenza vaccines by vaccine manufacturers represents

incremental progress towards more effective influenza vaccines, there remain significant technical challenges before a substantially better influenza vaccine is available. The discovery of new viral targets within the last four years has renewed interest and efforts to develop the long-sought-after “universal” influenza vaccine.

Because of the close scientific and technical connections between seasonal and pandemic influenza, developing better influenza vaccines is a top priority for BARDA. BARDA’s program to develop better influenza vaccines includes methods based on the field of evolutionary biology that may augment existing methods to forecast and select new seasonal and pandemic influenza vaccine strains. In parallel, we are launching this year an initiative to support advanced development of new influenza vaccine candidates that may elicit greater and broader immunity for all populations, longer duration of immunity, greater cross-protection against influenza virus variants, and that may serve as primers for pandemic influenza vaccines. To complement our goal to develop better influenza medical countermeasure, BARDA is adding immunotherapeutics or antibodies to our antiviral drug portfolio as a new approach to treat severe cases of influenza.

### **BARDA Accomplishments in Influenza Medical Countermeasures**

Since December 2005, HHS has been supporting fundamental medical countermeasures for seasonal and pandemic preparedness activities. Following the release of the Department’s *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Review* (2010) and the aforementioned PCAST report (2010), HHS made a mid-course adjustment and took steps to efficiently execute the pandemic influenza preparedness priorities enumerated in the review and report.

HHS has made significant progress improving vaccines and manufacturing technologies.

Specifically, BARDA has partnered with industry to achieve the following:

- Modernization of influenza vaccine manufacturing systems through the development and licensure of new cell- and recombinant-based influenza vaccines as well as antigen-sparing vaccines
  - Flucelvax (licensed 2012), the first cell-based seasonal influenza vaccine in the U.S.
  - FluBlÓk (licensed 2013), the first recombinant-based seasonal influenza vaccine in the U.S., and
  - Q-Pan H5N1 vaccine (licensed 2013), the first adjuvanted pandemic influenza vaccine in the U.S.
- With NIH, CDC, and FDA, we launched the Influenza Vaccine Manufacturing Improvement (IVMI) initiative, as recommended by PCAST to optimize the generation of high yielding vaccine seed strains and alternative potency and sterility assays, to expedite influenza vaccine availability. The IVMI initiative improvements cut weeks off the vaccine manufacturing process and increased production yields
- Establishment and maintenance of pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses with pandemic potential to rapid immunization of the critical workforce at the onset of an influenza pandemic; in parallel BARDA and CDC developed and implemented the Influenza Risk Assessment Tool (IRAT) in 2010 to inform the composition and prioritization of vaccines in this stockpile;
- Multi-fold expansion of domestic influenza vaccine production for pandemic preparedness by retrofitting older manufacturing plants (2007-2011) and building new state-of-the art, award-winning new manufacturing facilities (2009-2012) through BARDA's public-private partnerships with industry;

- Establishment of a national infrastructure to rapidly develop, manufacture, and test new influenza vaccines and medical countermeasures for emerging infectious diseases, such as Ebola. This infrastructure responded in 2013 with the development, production, testing, and stockpiling of H7N9 influenza vaccines and more recently Ebola vaccine and monoclonal antibody therapeutic candidates in 2014-2015. BARDA's national response infrastructure is comprised of the following programs:
  - Nonclinical Studies Network (2011) comprised of 17 laboratories able to perform animal testing;
  - Centers for Innovation in Advanced Development and Manufacturing (CIADM) (2012) comprised of three (3) government-industrial-academic consortia to develop and manufacture MCMs for CBRN threats routinely and in an emergency for pandemic influenza and emerging infectious diseases such as Ebola;
  - Fill Finish Manufacturing Network (FFMN) (2013) comprised of four (4) Contract Manufacturing Organizations to provide aseptic filling of medical countermeasures for CBRN threats, pandemic influenza, emerging infectious diseases, and possibly U.S. drug shortages (pilot program between FDA and BARDA);
  - Clinical Studies Network (2014) comprised of five (5) Clinical Research Organizations to provide clinical evaluation of medical countermeasures as needed for man-made and natural threats including Ebola currently.

The CIADMs and FFMN fulfilled the PCAST Report recommendation to expand and improve vaccine manufacturing capacity to meet the national goal of making the first dose of pandemic influenza vaccine available within 12 weeks of pandemic onset and to



ensure that sufficient quantities are available to meet national demand in less than six (6) months.

- Establishment of a global vaccine manufacturing infrastructure with the World Health Organization in 2006 in eleven (11) developing countries to make pandemic influenza vaccines and vaccines for other diseases resulting in four licensed influenza vaccines and a current capacity able to produce more than 300 million doses of pandemic influenza vaccine;
- Development of novel influenza antiviral drug candidates for treatment of influenza leading to the FDA approval (2014) of the first intravenously-administered, single dose influenza antiviral drug - Raptivab (peramivir), which was accessible under EUA during the 2009 H1N1 pandemic;
- Establishment of Federal and State stockpiles of influenza antiviral drugs and assistance to the CDC's Strategic National Stockpile in the maintenance of these stockpiles;
- Development and FDA clearance (2012) of a PCR-based rapid point-of-care clinical diagnostic (Simplexa) for detection of influenza and respiratory syncytial viruses. Similarly BARDA and CDC jointly developed rapid simple diagnostics for detection of seasonal and H5N1 viruses in point-of-care (POC) settings by health care providers and complex diagnostics for high throughput settings in State health and commercial clinical laboratories. and
- Development and FDA clearance (2012) of next generation portable ventilators (Aura).

### **HHS Influenza Improvements in Action – H7N9 Response (2013)**

The HHS response to the H7N9 avian influenza outbreaks exemplified Federal agency cooperation and public-private partnerships with industry building upon lessons learned from the 2009 H1N1 pandemic. The HHS interagency IRAT process determined that the risk from H7N9 was significant, and that it would be prudent to stockpile vaccine. BARDA played a key role in these HHS efforts including utilization of new cell- and recombinant-based flu vaccines developed with BARDA support. Secondly, H7N9 vaccine seeds using biosynthetic methods were developed by Novartis with BARDA support as a result of the technology derived from the HHS IVMI initiative to provide vaccines faster. Finally, the Novartis CIADM in Holly Springs, North Carolina played a major role in the development, manufacturing, clinical testing, and stockpiling of H7N9 vaccines in record time.

### **BARDA and the Future of Influenza Medical Countermeasures**

BARDA is working with NIH to foster collaborations with academia and industry in pursuit of more effective influenza vaccines. New evolutionary biology methods such as antigen cartography may be able to predict influenza virus evolution better and understand immune responses to the influenza viral hemagglutinin (HA) proteins from genetically-distinct viruses better. By generating specific and random influenza virus mutants to seasonal and pandemic influenza viruses, the evolutionary trend for new virus strains may be obtained and thus may inform vaccine strain selection. Using these results, future vaccine candidates may be designed using this forward-looking information and provide pre-emptive vaccination through what is called back-boost vaccine immunity. BARDA is supporting such studies to inform the

composition of pre-pandemic H5N1 and H7N9 vaccine stockpiles, as well as seasonal human vaccine strains.

The discovery in 2010-2011 that the conserved regions of the stalk of the influenza hemagglutinin protein, which is the major immunogenic component of influenza vaccines, could elicit protective immunity across many influenza virus strains has brought renewed interest into the development of new types of influenza vaccines or so-called “universal influenza vaccines” and monoclonal antibodies as new immunotherapeutics. Several current vaccine candidates including a chimeric HA stalk vaccine candidate are in early development supported jointly by BARDA and the NIH’s National Institute of Allergy and Infectious Diseases (NIAID). BARDA is launching a new advanced development program for more effective influenza vaccines this month. Based on these same discoveries, BARDA is starting a new program to support the advanced development of influenza immunotherapeutics to treat severe hospitalized cases of influenza.

### **Conclusion**

Influenza and other emerging infectious diseases with pandemic potential continue to mutate, evolve, and infect animals and humans, posing continued significant threats to global public health and to the United States. Together with our Federal and industry partners, we have made great strides towards pandemic influenza preparedness. Our Nation must continue to invest in domestic pandemic preparedness efforts and work with key global partners to prepare for, prevent, detect, and respond to emerging pandemic threats. This year’s limited seasonal influenza vaccine effectiveness and the arrival of the first human case of H7N9 virus in North America highlight our urgent need together with industry and academic partners to make better seasonal and pandemic influenza vaccines, antivirals, and diagnostics. ASPR and BARDA are

prepared to meet those challenges and provide resources, expertise, and technical assistance for these and other promising investigational vaccine and therapeutic candidates.