



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

**“The U.S. Public Health Response to Seasonal
Influenza”**

Statement of

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Introduction

Good morning Chairman Murphy, Ranking Member DeGette, and distinguished Members of the Subcommittee. Thank you for providing me the opportunity to speak with you today in regard to medical countermeasure (MCM) preparedness and response efforts for seasonal and pandemic influenza. 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) at the Department of Health and Human Services (HHS). I look forward to talking with you about our advancements in pandemic influenza vaccine preparedness and their positive influence on seasonal influenza vaccines.

Recognizing lessons learned from disasters including the terrorist attacks on 9/11, the anthrax attacks in 2001, and Hurricane Katrina, ASPR was established in 2006 to improve coordination and direction across the spectrum of HHS preparedness and response activities. Under the Public Health Service Act, as amended by the Pandemic and All-Hazards Preparedness Act (PAHPA) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), ASPR was established as the lead for HHS emergency preparedness and response and serves as the principal advisor to the Secretary regarding Federal public health and medical preparedness and response to public health emergencies. ASPR's responsibilities are broad and include: overseeing advanced research, development, and procurement of resulting medical countermeasures; coordinating with health care systems; and providing integrated policy and strategic direction under the National Response Framework. In addition, ASPR directs medical and public health grants and cooperative agreements, provides leadership in international programs and policies with global impact, and has developed and submitted a five-year budget

plan for countermeasure priorities. ASPR oversees the National Disaster Medical System (NDMS), the Hospital Preparedness Cooperative Agreement Program (HPP), and BARDA. Moreover, through guidance documents like the National Health Security Strategy (NHSS) and Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (SIP), ASPR leads the path forward for our partners and stakeholders.

Within ASPR, BARDA is the 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 to address the medical consequences of man-made chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring threats. Recent infectious disease threats that BARDA has responded include the 2009 H1N1 pandemic, the 2013 H7N9 influenza outbreak, the 2014-2015 Ebola epidemic, and current MERS-CoV endemic outbreaks.

By supporting advanced research and development of MCM candidates, BARDA addresses the medical consequences of threats and bridges the gap between early research and development and advanced development towards Food and Drug Administration (FDA) approval and potential procurement of these MCMs. Advanced development includes the critical steps necessary to transform an MCM candidate into a product that is ready to use. Since 2006, we have funded and successfully managed the advanced development of nearly 200 MCMs for CBRN threats, pandemic influenza, and emerging infectious diseases. Twenty two of these products have received FDA approval since 2007. We have also made available or stockpiled

twelve CBRN medical countermeasures under Project BioShield and 18 influenza medical countermeasures for the 2009 H1N1 and avian influenza H5N1 and H7N9 outbreaks.

Seasonal influenza epidemics occur every year. However, periodically a novel influenza virus strain, for which there is little human immunity, will emerge and cause a global pandemic like the 2009 H1N1 pandemic, or worse, the pandemic of 1918. Because influenza viruses mutate as they traffic and reassort primarily among birds, swine, and humans, 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 repeatedly reminded about the complexity of managing seasonal and pandemic influenza both globally and nationally. The most recent examples include the seasonal influenza vaccine mismatch to the antigenically-drifted H3N2 virus during the 2014-2015 influenza season and the avian influenza H5 viruses that killed millions of domestic birds in the Midwest earlier 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. Lessons learned from the H1N1 pandemic resulted in the President's Council of Advisors on Science and Technology's (PCAST's) *Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* (2010), which recommended improvements in virus surveillance, in vaccine research and development,

and in influenza vaccine manufacturing. As a call to action, HHS reviewed and revised existing 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 was that seasonal and pandemic influenza are inextricably interwoven; what we do in one area directly affects what we do in the other. Ten years after the HHS Pandemic Plan (2005) was issued, HHS is working to update the HHS Pandemic Plan based on our experiences with the 2009 H1N1 pandemic, the continual emergence of new avian influenza viruses with pandemic potential, and advancements we have made towards making more and better influenza vaccine sooner.

HHS, with its integrated and coordinated Federal agencies - the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Office of the Assistant Secretary for Health (OASH), FDA, and ASPR including BARDA - have partnered with industry, other governments, 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 seasonal influenza activities managed out of the National Vaccine Program Office in OASH. Within ASPR, BARDA is directly responsible for working with industry, academia, other governments, 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.

While the recent introduction of quadrivalent, high-dose, and novel seasonal influenza vaccines by vaccine manufacturers represents incremental progress towards more effective influenza vaccines, there remain significant technical challenges before a substantially more effective 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 ASPR. Our work to develop better influenza vaccines, including methods based on the field of evolutionary biology, may augment existing methods to forecast and select new seasonal and pandemic influenza vaccine strains. In parallel, we launched an initiative to support advanced development of more effective influenza vaccines that may elicit greater and broader immunity for all populations, longer duration of immunity, and greater cross-protection against influenza virus variants, and that may serve as primers for pandemic influenza vaccines. To accomplish our goal of developing better influenza medical countermeasures, we added immunotherapeutics or antibodies to our antiviral drug portfolio as a new approach to treat severe cases of influenza.

ASPR Accomplishments in Influenza Vaccines

Since December 2005, HHS has been supporting medical countermeasures for seasonal and pandemic preparedness activities. Following the release of the Department’s 2010 *PHEMCE Review* and the aforementioned PCAST report (2010), HHS made adjustments and took steps to

execute the pandemic influenza preparedness priorities enumerated in the review and report.

HHS has made significant progress improving vaccines and manufacturing technologies.

Specifically, we have 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 (2012), the first cell-based seasonal influenza vaccine in the United States
 - Flublok (2013), the first recombinant-based seasonal influenza vaccine in the United States
 - Q-Pan H5N1 vaccine (2013), the first adjuvanted pandemic influenza vaccine in the United States
 - Flud seasonal influenza vaccine (2015), recommended by the recent VRBPAC for licensure as an adjuvanted seasonal influenza vaccine for seniors in the United States;
- 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 may 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 rapidly immunize the critical workforce at

the onset of an influenza pandemic. In parallel, ASPR 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 manufacturing facilities (2009-2012) through a 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; and
- Establishment of a global vaccine manufacturing infrastructure with the World Health Organization (WHO) in 2006 in eleven (11) developing countries to make pandemic influenza vaccines and vaccines for other diseases. This initiative has resulted in the establishment of manufacturing facilities making four licensed influenza vaccines with a current capacity to produce 300 million doses of pandemic influenza vaccine.

HHS Influenza Improvements in Action – Seasonal Influenza Vaccines (2015)

HHS responded to the H3N2 antigenic drift and seasonal influenza vaccine mismatch in 2014-2015 by tasking the Department's senior influenza leaders and experts last winter to provide a comprehensive set of recommendations to the HHS Secretary on how to address the issue of vaccine mismatch in the near and long term. HHS convened numerous meetings from December

2014 through May 2015 with internal and external influenza and vaccine experts from government, industry, and academia to understand the complexities of virus antigenic drift, vaccine mismatch, and influenza vaccine manufacturing and how seasonal vaccines and their manufacturing may be changed to accommodate this type of virus variance. In May 2015, senior HHS influenza leaders provided a set of twenty (20) recommendations to HHS leadership that may improve virus surveillance and characterization, vaccine design, vaccine manufacturing, vaccine availability and distribution, and ultimately vaccine effectiveness. In June 2015, ASPR hosted a meeting with the influenza vaccine manufacturers constituting the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and with representatives from the WHO, the government of the United Kingdom, HHS agencies, and others to review current influenza epidemiology. This review was relative to the current seasonal influenza vaccine, the HHS recommendations for improving responses to seasonal influenza vaccine mismatches, an exercise scenario similar to the 2014-2015 seasonal influenza antigenic drift and vaccine mismatch, and the current timelines for production of a new seasonal influenza vaccine and what improvements could be made to reduce those timelines.

From these recommendations and exchanges with U.S. and international public and private stakeholders, HHS developed an action plan to address vaccine mismatch for seasonal influenza. Many of these recommended actions stemmed from ongoing pandemic influenza preparedness activities such as the IVMI initiative and universal influenza vaccine development. Several of these seasonal influenza vaccine improvement actions are being implemented over the next year. One already in place involves earlier and more frequent communication on antigenic changes in circulating influenza viruses during the year from CDC to senior leaders at HHS, FDA, WHO,

vaccine manufacturers, and between FDA and the Chair of VRBPAC. Several advances derived from pandemic influenza vaccine preparedness are being transitioned by CDC and FDA into the development of seasonal candidate vaccine viruses and seasonal vaccine potency reagents with vaccine manufacturers. Implementation of the other action items is also underway to reach intermediate and long term goals. Many of the immediate actions were evaluated in a recent exercise with HHS agencies, WHO, representatives from other countries, and vaccine manufacturers. The exercise was expected to indicate whether these recommended actions would have a significant impact on improving seasonal influenza vaccines. In addition, the exercise was expected to show how the United States, WHO, other countries, and vaccine manufacturers could manage virus antigenic drift and vaccine mismatches better.

The Future of Influenza Vaccines

ASPR 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 understood better and thus may inform vaccine strain selection. With these results, future vaccine candidates may be designed using this forward-looking information and may provide more effective vaccines through what is called “back-boost” vaccine immunity. We are also supporting such studies to inform the composition of pre-pandemic vaccine stockpiles, as well as seasonal human vaccine strains.

The 2010-2011 discovery that the conserved regions on 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). This year we launched a new advanced development program for more effective influenza vaccines with universal potential and awarded one contract in September 2015 to support development of a novel influenza vaccine candidate.

Conclusion

Influenza and other emerging infectious diseases with pandemic potential continue to mutate, evolve, and infect animals and humans, posing significant threats to global public health and to the United States. Together with our Federal and industry partners, ASPR has made great strides towards pandemic influenza preparedness. While we have made progress in leveraging the improvements achieved for pandemic influenza vaccine manufacturing to benefit our seasonal vaccine needs, overall success in improving season readiness is dependent on the introduction and implementation of new technologies and new vaccines through the engagement and coordination of all stakeholders and partners including government, surveillance systems, industry, the World Health Organization and others. Last year’s limited seasonal influenza vaccine effectiveness and the arrival of the avian influenza H5 viruses in the Midwest highlight

our urgent need to prioritize the necessary resources to make better seasonal and pandemic influenza vaccines. ASPR is prepared to meet those challenges and provide resources, expertise, and technical assistance for these and other promising investigational vaccine candidates.