



Assistant Secretary for
Preparedness & Response
Washington, D.C. 20201

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your letter concerning our nation's stockpile of pre-pandemic vaccines. As the Assistant Secretary for Preparedness and Response (ASPR) within the Department of Health and Human Services (HHS), I appreciate the Committee's attention and commitment to preparedness and response issues, particularly related to pandemic influenza among many other important issues. While I missed the opportunity to testify before the Subcommittee on Oversight and Investigations on November 19, 2015, I am grateful Dr. Robin Robinson, ASPR's Director of the Biomedical Advanced Research and Development Authority (BARDA), was able to speak on my behalf and answer your questions.

As addressed in the hearing entitled, "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" influenza viruses can be difficult to predict and manage. Rest assured, the Department takes all influenza virus threats very seriously. We manage a multi-pronged approach to prepare for the emergence of new viruses and to thwart the potential spread of influenza to humans from poultry and other animals. Moving forward, advances in vaccines, new antiviral medications, and new diagnostic tests are just some of the ways HHS and ASPR have taken on the challenge of pandemic influenza preparedness. Likewise, public-private partnerships with industry have also led to cost savings and a surge in the nation's ability to produce vaccines and drugs for influenza and other health threats.

The safety and well-being of the American people is of the utmost importance. I thank you again for the opportunity to address your questions and I look forward to continuing our work with you and the Committee towards this important goal.

With that said, I have enclosed detailed responses to the questions in your letter. If you have any additional questions, please do not hesitate to contact me.

Sincerely,

Nicole Lurie, MD, MSPH

Enclosure

- 1. What are the results of testing BARDA has done on stockpiled pandemic vaccines? Please provide the committee with a list of the tests and the most recent data collected from these tests. How does BARDA evaluate these results in the context of the periodic risk assessments conducted by the HHS Influenza Risk Management Working Group or other HHS experts?**

Potency and sterility assays are used for all influenza vaccines licensed in the United States (U.S.) by the Food and Drug Administration (FDA). Potency and product sterility tests are performed on bulk and final product vaccine antigens and adjuvants throughout the national pre-pandemic influenza vaccine stockpiles managed by ASPR/BARDA. The influenza vaccine antigen potency assay, which measures the amount of active hemagglutinin protein - the major viral component conferring immunity - is performed by each manufacturer and the FDA using a serial radial immunodiffusion assay (SRID) specific for each influenza vaccine strain (e.g., A/H5N1/2004/Vietnam). These tests are conducted at three- to six-month intervals by three vaccine manufacturers [Sanofi Pasteur, GlaxoSmithKline (GSK), and Commonwealth Serum Laboratories (CSL, formerly Novartis Vaccines Division)]. The adjuvant potency assays measure the amount of active molecules (e.g., squalene and vitamin E) in the adjuvant that stimulate immunity. They are performed by the manufacturers using high-performance liquid chromatography (HPLC) and photometry tests specific for each of the stockpiled oil-in-water emulsion adjuvants (AS03 and MF59).

The most-recent test results in 2015 (Table 1) show that the potency and sterility of the stockpiled A(H5N1) and A(H7N9) vaccine antigens and MF59 and AS03 adjuvants are acceptable for formulation into final vaccine products, if needed, as there is enough stockpiled vaccine antigen and adjuvant to immunize at least 20 million persons against each vaccine strain.

In addition, the National Institutes of Health (NIH), through the National Institute of Allergy, Immunology, and Infectious Diseases (NIAID) has continued to conduct a series of clinical trials of stockpiled H5N1 and H7N9 vaccines with and without MF50 and AS03 adjuvants. While the primary focus of the NIAID clinical trials has been to assess different vaccination strategies and to advance our understanding of the breadth and duration of the immune response, the clinical study results also show that these stockpiled vaccines continue to be well tolerated and immunogenic in humans.

ASPR/BARDA and other HHS agencies routinely review the results of risk assessments using the Centers for Disease Control and Prevention's (CDC) Influenza Risk Assessment Tool (IRAT) on newly emerged novel influenza viruses with pandemic potential. Pandemic risk is based on two risk scenarios: emergence (acquiring the ability to spread easily and efficiently in people) and the public health impact (potential severity of human disease caused by the virus and the burden on society after emergence). The IRAT focuses on virological assessment and prioritization and more closely aligns with a multi-criteria or multi-attribute decision analysis approach. The risk elements addressed in the IRAT are listed below.

- **Properties of the virus**
 - Transmission in lab animals
 - Receptor binding
 - Genomic variation
 - Antiviral treatment susceptibility/resistance
- **Attributes of the population**
 - Antigenic relationship to vaccine candidates
 - Existing population immunity
 - Disease severity and pathogenesis
- **Ecology and epidemiology**
 - Human infections
 - Infection in animal species

The Influenza Risk Management group evaluates the vaccine potency results of stockpiled material, the antigenic relatedness of stockpiled vaccines to new influenza viruses, and the IRAT results for severity (impact) and transmissibility of new influenza viruses. These assessments inform decision makers on whether or not to replenish existing vaccine stockpiles, add additional vaccine, or include new candidate vaccine viruses.

Table 1. Results of potency and sterility assays in 2015 for bulk influenza vaccine antigens and adjuvants in the U.S. national pre-pandemic influenza vaccine stockpile.

Product	Manufacturer	Potency Assay Results	Sterility Assay Results ¹
Vaccine Antigens			
A/H5N1/ Vietnam/1203/ 2004	sanofi pasteur Novartis	56% 55-58%	Negative Negative
A/H5N1/Indonesia/05/2005	sanofi pasteur GSK	89% 78-100%	Negative Negative
A/H5N1/Bar Headed Goose/Qinghai Lake/1/2005	sanofi pasteur	57%	Negative
A/H5N1/Anhui/2008	Novartis	57%	Negative
A/H7N9/Shanghai/2013	sanofi pasteur	75%	Negative
	GSK	80%	Negative
	Novartis	60%	Negative
Adjuvants			
MF59	Novartis	Within specifications	Negative

AS03	GSK	Within specifications	Negative
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¹ Sterility result definitions for 14-day standard growth assay. Positive result indicates contamination observed. Negative result indicates no contamination observed.

- 2. BARDA's testimony discussed BARDA's plans to also test these stockpiles for potency. What were the results of these tests? Were additional tests conducted to determine if the vaccines in the stockpile are well matched to the current threats?**

Please see the response to question 1 regarding the test results of vaccine potency, specifically **Table 1**. CDC routinely performs antigenic and genetic characterization of circulating influenza viruses. When new influenza viruses emerge, CDC conducts further studies using reference animal-sera to evaluate how similar these viruses are to those represented by stockpiled vaccines. Typically, when antigenic differences are observed, this prompts the development of a Candidate Vaccine Viruses (CVV) that would provide better protection against the novel virus.

- 3. In your July 31, 2015 letter to the committee, you wrote that "[a]s a direct outcome of the IRAT (Influenza Risk Assessment Tool) process, the agencies [ASPR/BARDA and CDC] are conducting multiple scientific studies to determine whether previously stockpiled H5N1 vaccines confer immunity against HPAI [Highly Pathogenic Avian Influenza] H5 viruses in humans." Are any of the studies completed? If so, what were the findings? If not, when are the studies expected to be completed?**

In 2015, CDC evaluated whether or not stockpiled vaccine antigens (A/H5N1/Indonesia/05/2005 or A/H5N1/Anhui/01/2005) when combined with an adjuvant induced cross-reactive antibody responses to H5Nx viruses. This evaluation used a homologous prime-boost vaccination strategy (i.e., persons received two doses of the same vaccine). Minimum to no cross-reactive antibodies for A(H5N8) and A(H5N2) viruses were detected by microneutralization assays with sera from three H5N1 vaccine clinical studies (two A/H5N1/Indonesia/05/2005 studies and one A/H5N1/Anhui/01/2005 study).

In more recent studies, CDC evaluated whether or not stockpiled H5N1 vaccines (A/H5N1/Anhui/01/2005 and A/H5N1/Vietnam/1203/2004) produced cross-reactive antibody responses to newly emerging A(H5N2) and A(H5N8) viruses (clade 2.3.4.4) using a heterologous prime-boost vaccination strategy. Following one or two doses of non-adjuvanted A(H5N1) vaccine (A/H5N1/Vietnam /1203/2004) as a primer and one dose of adjuvanted A(H5N1) vaccine (A/H5N1/Anhui/1/2005) as a booster, modest levels of cross-reactive antibody responses to A(H5N8) and A(H5N2) viruses were detected. These results suggest that vaccinations primed with an older version of stockpiled H5N1 vaccines and an added booster A/Anhui/1/2005 vaccine, may elicit potentially cross-protective responses against the recent HPAI H5N8/H5N2 viruses. CDC has initiated vaccination and challenge studies using ferrets to determine if stockpiled vaccines will protect against the A(H5N8)/A(H5N2) viruses, and the results of these experiments will be available March 2016.

ASPR/BARDA submitted an Investigational New Drug (IND) application to the FDA on November 20, 2015, for a clinical study to determine whether previously stockpiled vaccines [A/H5N1/Vietnam/1203/2004] manufactured in 2005 and 2007 with MF59 adjuvant manufactured in 2009 and 2013 are still immunogenic. The FDA reviewed and accepted the IND application. The clinical study is set to start in March 2016. Preliminary interim results on immunogenicity should be made available by July 2016. Sera from subjects immunized with different amounts of the older and newer H5N1 vaccine and adjuvant lots will be used in hemagglutination inhibition assays and microneutralization assays to determine the relative antibody levels elicited to homologous vaccine virus (A/H5N1/Vietnam/1203/2004) and other H5N1 viruses.

NIH/NIAID has continued to conduct clinical trials to assess the safety and immunogenicity of stockpiled H5N1 and H7N9 vaccines administered with and without adjuvants. Several studies have been completed and published, while others are ongoing (please also see response to question 1).

4. What is the status of efforts by HHS agencies and vaccine manufacturers to develop, manufacture, and test new vaccine candidates to H5N2 and/or H5N8 viruses using egg- and cell-based influenza vaccine platforms to supplement existing stockpiled vaccines?

CDC developed a recombinant candidate vaccine virus specific to the North American A(H5N8) HPAI viruses that emerged in late 2014 and the A(H5N2) HPAI viruses that caused widespread poultry outbreaks in spring and summer 2015. The A/gyrfalcon/Washington/41088-6/2014 (H5N8)-like “IDCDC-RG43A” virus is the recombinant A(H5N8) candidate virus that represents the viruses found in North America in 2014-2015. It was recommended for development by the World Health Organization. CSL, under contract to ASPR/BARDA, prepared clinical investigational lots of the H5N8 vaccine candidate. These will be released when SRID potency assay reagents become available.

CDC developed candidate vaccine viruses (CVVs) to the A(H5N2) viruses, which caused the majority of poultry outbreaks across the U.S. in 2015. This candidate vaccine virus “IDCDC-RG47B” is an A/gyrfalcon/Washington/41088-6/2014-like virus developed to express the H5 hemagglutinin and the N2 neuraminidase genes from representative A(H5N2) viruses found in North America in 2015. Complete characterization of this virus, including ferret pathotyping, is in progress. If the CVV passes characterization CSL will produce clinical investigational lots in 2016 for future clinical studies.

NIH/NIAID, through its clinical research network, is preparing to start clinical trials to assess the safety and immunogenicity of different concentrations of an H5N8 vaccine administered with and without adjuvants in the second quarter of 2016.

5. Are there any studies that show the effects of long-term storage on the potency of influenza vaccines? If yes, what do the studies show? If not, what is the basis for our

understanding about the potency of influenza vaccines? At what point, would the vaccines lose potency?

Yes, potency studies have been performed continuously on all lots of stockpiled, pre-pandemic H5N1 and H7N9 vaccine antigens. These studies have been performed since the lots were manufactured and will continue. The results of these potency assays have indicated that some of the influenza vaccine antigens (e.g., A/H5N1/Vietnam/1203/2004) undergo an initial diminution (20-25 percent) of potency within the first three to six months then stabilize with gradual losses in potency over years (Fig. 1). However, the vaccine potency of other A(H5N1) strains (e.g., A/H5N1/Indonesia/05/2005) decrease very slowly and retain nearly all of its original potency (Fig. 1). The vaccine virus, the manufacturer, and the manufacturing process affect the potency of stockpiled A(H5N1) vaccines.

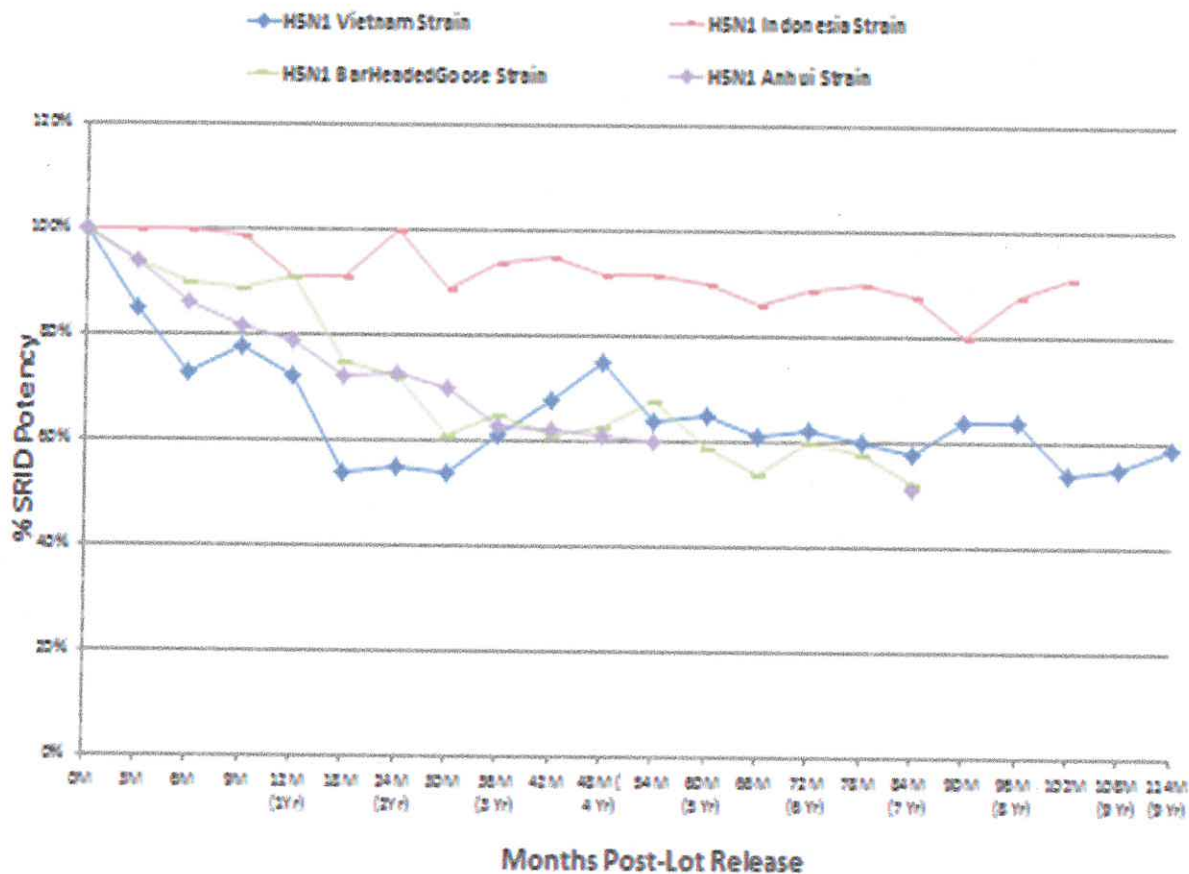


Figure 1. Vaccine SRID potency assay results of stockpiled H5N1 vaccine antigens from 2006–2015.

6. What kind of testing of the pre-pandemic stockpile is needed on an ongoing basis and what funding is needed to support this kind of testing?

Potency and sterility testing of stockpiled bulk and final container vaccine antigens and adjuvants are performed on three- to six-month intervals throughout the storage of these products. Vaccines are tested periodically in animal and clinical studies. Funding (\$1 million to \$2 million per year) for potency and sterility testing of these products at the vaccine manufacturers is provided by HHS through ASPR/BARDA contracts using pandemic influenza supplemental appropriations (2005), H1N1 supplemental appropriations (2009), or annual pandemic influenza funds (2013-2015). Animal and human serology studies (\$200,000 to \$250,000 per study) are conducted at CDC using annual CDC funds. Clinical studies (\$2 million to \$5 million per study) are performed by NIH/NIAID, BARDA's Clinical Study Network, or vaccine manufacturers using supplemental or annual funds, depending on the fiscal year fiscal year during which the study is performed.

7. At the CDC's ACIP meeting in June 2015, a CDC official showed data indicating that the stockpiled vaccines do not protect against the current circulating avian strains, and may be distantly related to the viruses. How many doses of the vaccine are in the BARDA stockpile contain the Anhui strain that is more closely related to the currently circulating avian strains? Has there been any testing of the vaccines with the Anhui strains on how well they protect against the currently circulating avian strains?

Recent outbreaks of HPAI viruses in U.S. poultry (December 2014 to June 2015) have raised public health concerns. Three novel subtypes of viruses [A(H5N8), A(H5N2), and A(H5N1)] have been identified in infected birds in the U.S. All three subtypes have a Eurasian (HA) lineage and are designated as H5Nx (clade 2.3.4.4). In 2015, CDC evaluated whether or not stockpiled vaccine antigens (A/H5N1/Indonesia/05/2005 or A/H5N1/Anhui/01/2005) when combined with an adjuvant induced cross-reactive antibody responses to H5Nx viruses. This evaluation used a homologous prime-boost vaccination strategy (i.e., persons received two doses of the same vaccine). Minimum to no cross-reactive antibodies for A(H5N8) and A(H5N2) viruses were detected by microneutralization assays with sera from three H5N1 vaccine clinical studies (two A/H5N1/Indonesia/05/2005 studies and one A/H5N1/Anhui/01/2005 study).

In more recent studies, CDC evaluated whether or not stockpiled H5N1 vaccines (A/H5N1/Anhui/01/2005 and A/H5N1/Vietnam/1203/2004) produced cross-reactive antibody responses to newly emerging A(H5N2) and A(H5N8) viruses (clade 2.3.4.4) using a heterologous prime-boost vaccination strategy. Following one or two doses of non-adjuvanted A(H5N1) vaccine (A/H5N1/Vietnam/1203/2004) as a primer and one dose of adjuvanted A(H5N1) vaccine (A/H5N1/Anhui/1/2005) as a booster, modest levels of cross-reactive antibody responses to A(H5N8) and A(H5N2) viruses were detected. These results suggest that vaccinations primed with an older version of stockpiled H5N1 vaccines and an added booster A/Anhui/1/2005 vaccine, may elicit potentially cross-protective responses against the recent

HPAI H5N8/H5N2 viruses. CDC has initiated vaccination and challenge studies using ferrets to determine if stockpiled vaccines will protect against the A(H5N8)/A(H5N2) viruses, and the results of these experiments will be available in March 2016.

Studies are planned using human sera from clinical subjects that were vaccinated with an adjuvanted prime dose of A(H5N1) vaccine (A/H5N1/Vietnam /1203/2004), followed by an adjuvanted A(H5N1) vaccine (A/H5N1/Anhui/1/2005) - **adjuvanted heterologous** prime-boost approach to assess cross-reactive antibody responses to newly emerging A(H5N2) and A(H5N8) viruses. These studies may show cross-reactivity of stockpiled A(H5N1) vaccines to more currently circulating H5 viruses. Results from previous adjuvanted heterologous prime-boost approaches in H5N1 vaccine clinical trials show strong immunity to the viruses in the vaccine and some have demonstrated cross-reactivity to other A(H5N1) virus.

8. What assumptions is BARDA using to determine if/how well the current pre-pandemic stockpiles will protect the public on the event of a pandemic?

The safety and protective immunity afforded by seasonal influenza vaccines manufactured by different processes – egg-, cell-, and recombinant-based – provide the basis for the effectiveness of pre-pandemic and pandemic influenza vaccines. Additionally, results from more than 100 clinical studies conducted worldwide using A(H5N1) vaccine candidates since 2005 have shown that the stockpiled H5N1 vaccines and adjuvants are well-tolerated, highly immunogenic, and cross-reactive among H5 virus subclades at seroprotective titers. As licensed by FDA in 2013, ID Biomedical Corporation of Quebec's (a subsidiary of GlaxoSmithKline) Influenza A(H5N1) Virus Monovalent Vaccine, Adjuvanted vaccine (A/H5N1/Indonesia/2005 vaccine antigen with the AS03 adjuvant) is now part of the federal pre-pandemic influenza stockpile.

9. How do issues like the age of the stockpile and possible mismatch against currently circulating pandemic strains affect these determinations?

At least once a year since 2011, HHS has conducted risk assessments of newly emerging and existing novel influenza viruses with pandemic potential. Assessments are made utilizing CDC's IRAT and evaluate disease severity, transmissibility in animals, and antigenic and genetic relatedness to stockpiled vaccines. Using a multi-attribute analytical process, these results are combined with the most recent potency results of each lot of stockpiled vaccine antigens and adjuvants. This is done to inform HHS decisions about whether or not to add more vaccine for existing and/or new influenza virus strains. Results get reported in the first quarter of each year. For example, in 2013 new A(H7N9) vaccine antigens were developed, manufactured, tested, and stockpiled due to the risk of high mortality and potential transmission of this virus in humans, as well as the absence of any immunogenic H7 vaccine candidates. In 2008, the quantities of vaccine for the A/H5N1/1204/Vietnam/2004 virus needed to be replaced in the stockpile due to the lowered potency of lots manufactured in 2005. This resulted in the total amount of stockpiled vaccine antigen being insufficient to immunize 20 million people.

10. Are pandemic influenza risk assessments provided to key stakeholders?

The HHS IRAT process involves many key influenza and vaccine scientists in academia, government, and industry throughout the world to provide opinions on the severity and transmissibility of existing and newly emerging novel influenza viruses with pandemic potential. ASPR/BARDA informs vaccine manufacturers about the IRAT results each year in discussions about requirements to develop, manufacture, and test influenza vaccines for potential task orders on existing contracts. IRAT results and U.S. pre-pandemic influenza vaccine stockpiling information are presented at many public scientific and government meetings with key industry stakeholders, including conferences hosted by the International Federation of Pharmaceutical Manufacturers & Associations and BARDA Industry Day.

The HHS IRAT process involves many key influenza and vaccine scientists in academia, government, and industry worldwide who provide assessments on the severity and transmissibility of existing and newly emerging novel influenza viruses with pandemic potential. ASPR/BARDA conveys these IRAT results each year to manufacturers in discussions about requirements to develop, manufacture, and test influenza vaccines for potential task orders on existing contracts. IRAT results and U.S. pre-pandemic influenza vaccine stockpiling information are presented at many public scientific and government meetings with key industry stakeholders, including conferences hosted by the International Federation of Pharmaceutical Manufacturers & Associations and BARDA Industry Day.

11. Given the existing contingency pandemic influenza vaccine stockpiles are aging – most are 5-10 years old – what resources does BARDA need on annual basis to update the stockpile and prepare for the next pandemic threat?

During establishment of the pre-pandemic influenza vaccine stockpile between 2005 and 2013, ASPR/BARDA utilized funds from the Pandemic Influenza (2005) and H1N1 (2009) supplemental appropriations. Since 2014, ASPR/BARDA has reserved between \$20 million and \$25 million of the annual HHS pandemic influenza budget for storage, testing, and replenishment, as well as additions to, the national pre-pandemic influenza vaccine stockpile. When a new influenza virus with significant pandemic potential emerges (e.g., the A(H7N9) virus in China in 2013), supplemental appropriations (\$150 million) are used to develop, manufacture, test, and stockpile vaccines.

12. If a rapid MCM response was required to address a seasonal influenza epidemic due to a mismatched vaccine, does BARDA have resources to respond? If so, how? Are resources available to support availability of a matched vaccine?

If a new seasonal influenza vaccine was deemed necessary to address a vaccine mismatch, FDA and CDC would serve as the primary HHS agencies that would work with vaccine manufacturers to produce better-matched seasonal influenza vaccines by providing new CVVs and vaccine potency assay reagents. Both NIH/NIAID and ASPR/BARDA would provide assistance to the

vaccine manufacturers to evaluate the safety and immunogenicity of these better-matched seasonal influenza vaccines in clinical studies. Resources would be needed by all HHS agencies to develop and test these vaccines. Presumably, the better-matched seasonal influenza vaccines would be sold by the manufacturers through usual market and reimbursement mechanisms.

13. How does BARDA plan to maintain and replenish the stockpile of influenza vaccines, some of which are now a decade old? What funds are planned to be used?

Please see the response to question 11.

14. Are current stockpiles consistent with the national Strategy for Pandemic Influenza which states the U.S. should have sufficient vaccine to vaccinate the entire population within six month of the emergence of a virus with pandemic potential?

The current stockpiles of pre-pandemic influenza vaccine meet the goal set in the National Strategy for Pandemic Influenza (2005) - sufficient stockpile for the critical workforce. The federal government in 2008 estimated that the number of people in the critical workforce is between 20 million and 23 million. The H5N1 vaccine stockpiles could provide vaccine for 100 million to 200 million people, depending on the antigenic and genetic relatedness of the emerging virus with the stockpiled vaccine and the amount of antigen used with adjuvant. The H7N9 vaccine stockpile could provide vaccine for 20 million to 30 million people.

The strategic goal of providing sufficient pandemic influenza vaccine to meet U.S. needs within six months has been made possible through our public-private partnerships with industry since 2005. These partnerships have allowed us to expand domestic manufacturing capacity for pandemic influenza vaccines through development and implementation of modern vaccine manufacturing processes. This is possible thanks to the development and use of cell-and recombinant-based technologies and adjuvant technologies. It also includes cost-share partnering for retrofitting vaccine manufacturing facilities, building new facilities, and by establishing the Centers for Innovation in Advanced Development and Manufacturing and the Fill Finish Manufacturing Network. Additionally, NIH/NIAID, CDC, and ASPR/BARDA are supporting the development of more effective influenza vaccines. These efforts include vaccine candidates that may provide better immunity against seasonal epidemics and those that may provide broader-based immunity against influenza viruses with pandemic potential.

15. What level of annual funding would be sufficient, going forward, to maintain and replenish the stockpile, in order to ensure U.S. preparedness against pandemic influenza? Please detail how these funds would be spent.

Since 2014, ASPR/BARDA has reserved \$20 million to \$25 million of the annual HHS pandemic influenza budget for storage, testing, and replenishment of the U.S. national pre-pandemic influenza vaccine stockpile. When a new influenza virus with significant pandemic potential emerges, like the 2013 A(H7N9) virus, supplemental appropriations (\$150 million) are

used to develop, manufacture, test, and stockpile vaccines. In our multi-year budget for influenza, we estimate that \$50 million a year may be needed to maintain these stockpiles for fiscal years 2018 and 2019. This money would be used to replace existing vaccine antigens and adjuvants and to address any new vaccines that may need stockpiling.