



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
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STATEMENT

OF

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**FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

BEFORE THE

**SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES**

**“U.S. Public Health Preparedness for Seasonal Influenza: Has the Response
Improved?”**

November 19, 2015

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, Ranking Member DeGette, and Members of the Subcommittee, I am Dr. Karen Midthun, Director of the Center for Biologics Evaluation and Research (CBER), which is the Center in the Food and Drug Administration (FDA or the Agency) responsible for regulating vaccines. Thank you for the opportunity to be here today to discuss FDA's role in the highly collaborative, multi-partnered effort in preventing influenza through vaccination in the United States.

Influenza is a major public health concern that annually causes illness in a substantial proportion of the U.S. population and may result in serious complications, including hospitalization and death. Influenza viruses are highly unpredictable, and each year can present new challenges for vaccine manufacturers, public health agencies, the medical community, and patients. This year there is a record amount of influenza vaccine available, which continues to be antigenically well-matched to viruses that have been circulating to date. It is estimated that 171-179 million doses of vaccine will be available for the 2015-2016 influenza season. In 2015, there are seven U.S.-licensed manufacturers who make 14 licensed seasonal influenza vaccines, including some vaccines manufactured using novel technologies.

Influenza viruses continually undergo changes in their genetic makeup and the resulting proteins that interact with the immune system. These changes can occur from one season to the next; they can also occur within the course of an influenza season. Unlike other vaccines, the composition of influenza vaccines must be periodically updated so that they are effective against

what are anticipated to be the predominant circulating viruses in the upcoming influenza season. The strains of virus used in vaccine production include two distinct subtypes of influenza A (H1N1 and H3N2) and one (for trivalent vaccine) or two (for quadrivalent vaccine) different lineages of influenza B (B/Yamagata and B/Victoria, which are genetically divergent from each other).

Virus Strain Selection—A Worldwide Process to Ensure the Timely Availability of Influenza Vaccine

The process of ensuring the timely availability of influenza vaccine in the United States and elsewhere is a global, year-round process. Each year, the World Health Organization (WHO) convenes technical consultations in February and September to recommend the virus strains for inclusion in influenza vaccines for the Northern and Southern Hemispheres, respectively. FDA participates in both of these technical meetings. To identify virus strains likely to cause illness during the upcoming influenza season, influenza experts from WHO Collaborating Centers for Influenza (which include the Centers for Disease Control and Prevention (CDC)), the WHO Essential Regulatory Laboratories (which include FDA's CBER), and other influenza and public health experts study recently circulating influenza viruses from around the world and recent global disease patterns. In addition, blood samples from individuals receiving the most recent influenza vaccines are analyzed by the WHO Essential Regulatory Laboratories and WHO Collaborating Centers to determine how well antibodies induced by these vaccines react to recently isolated viruses. After careful evaluation of the antigenic and genetic characteristics of influenza viruses that are circulating and infecting humans across the globe and the ability of current vaccines to protect against these viruses, WHO makes recommendations on the composition of the influenza vaccines for use in the upcoming influenza season. These

recommendations are taken into account by national vaccine regulatory agencies, such as FDA, and vaccine manufacturers as they consider the vaccine composition for the upcoming season. WHO usually makes its vaccine strain recommendations in February for the upcoming influenza season in the Northern Hemisphere and in September for the upcoming influenza season in the Southern Hemisphere. The recommendations must be made months in advance of the next influenza season because of the time required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses consisting of antigens derived from three or four different influenza virus strains.

FDA's Role and the Manufacturing Process

WHO recommendations resulting from the technical consultations described above provide a guide to national public health authorities and vaccine manufacturers for the development and production of influenza vaccines for the upcoming influenza season. In the United States, FDA is responsible for regulating vaccines. In this role, FDA brings together public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines. FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) each year, typically in late February or early March and within a few weeks after the WHO consultation on influenza vaccine composition.

The VRBPAC considers the recommendations made by the WHO regarding the composition of influenza vaccines for the upcoming influenza season in the Northern Hemisphere. The committee also reviews information regarding viruses that have caused human illness in the previous year, how these viruses are changing, and disease trends. The information considered

in the review is provided in large part by CDC and WHO laboratories throughout the world. Based on the data available at the time of the meeting, the Advisory Committee makes a recommendation for the composition of influenza vaccines licensed by FDA for use in the United States during the upcoming season.

High growth candidate influenza viruses, which have been generated and accepted by WHO collaborating centers, are provided to the licensed vaccine manufacturers to generate the “seed viruses” for manufacturing their influenza vaccines. FDA confirms the antigenic suitability of the manufacturer’s seed viruses. The manufacturing demands for influenza vaccines are substantial; there is no other vaccine that has to be produced, FDA-approved, and distributed every year across the United States within a six-month time frame. The manufacturing timelines are tight and the process of producing influenza vaccine involves many sequential steps and overlapping processes. Even with technologic advancements, each of these steps and processes still requires time to complete. Given the yearly need for a new vaccine, there is limited flexibility in the timelines for influenza vaccine production and availability.

Manufacturing of each antigen to be included in the vaccine occurs sequentially over several months, usually from December (produced at risk by the manufacturer before the strain recommendations are made) until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents which are provided to the vaccine manufacturers and our regulatory counterparts throughout the world. Manufacturers and FDA use these reagents to test the vaccines for potency and identity before FDA approves the new formulation of the licensed seasonal influenza vaccines for U.S. distribution. The vaccines are formulated into standard

dosages, filled and finished by the manufacturers into final containers such as vials, syringes, and sprayers. Manufacturers submit their vaccine testing results, along with samples from each lot, to FDA for “lot release.” As FDA releases lots, the manufacturers can make these lots commercially available throughout the United States. Typically, FDA approves the updated seasonal influenza vaccines with new labeling by the end of July. Every year, FDA begins working with manufacturers at the earliest stages of influenza vaccine development, and we continue to assist them throughout the production phase. During this period, we engage the companies on technical and manufacturing issues and conduct facility inspections to ensure compliance with good manufacturing practice, as warranted.

2015-2016 Influenza Season

FDA's VRBPAC met on March 4, 2015, to select the influenza viruses for the composition of the influenza vaccine for the 2015-2016 U.S. influenza season. During this meeting, the Advisory Committee reviewed and evaluated the surveillance data related to epidemiology and antigenic characteristics of recent influenza isolates, serological responses to 2014-2015 vaccines, and the availability of candidate strains and reagents. The Committee recommended that the trivalent influenza vaccines for the U.S. 2015-2016 influenza season be produced with the following: an A/California/7/2009 (H1N1)-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like virus. The Committee also recommended that quadrivalent influenza vaccines be produced with the above three strains and the following additional B strain: a B/Brisbane/60/2008-like virus.

As noted earlier, the influenza vaccine continues to be antigenically well-matched to viruses that have been circulating to date, based on surveillance and testing conducted by CDC and other WHO Collaborating Centers. Manufacturers have projected that they will provide approximately 171 to 179 million doses of vaccine for the U.S. market, a record amount.

Department of Health and Human Services (HHS) Preparedness Efforts in the Event of a Future Seasonal Influenza Vaccine Mismatch

As part of the efforts to improve public health emergency preparedness for seasonal and pandemic influenza, HHS staff with expertise in influenza convene monthly at the Pandemic and Seasonal Influenza Risk Management Meeting (also known as the Flu Risk Management Meeting (FRMM)). Participating agencies include HHS (ASPR, the Biomedical Advanced Research and Development Authority (BARDA), the Assistant Secretary for Health's National Vaccine Program Office, FDA, the National Institutes of Health (NIH), and CDC), the Department of Homeland Security, and the Department of Veterans Affairs. This group deliberates policy and programmatic issues regarding influenza medical countermeasures. Discussions include an end-to-end approach from basic research to the advanced development of new medical countermeasures to distribution and utilization strategies.

In response to the mismatch that occurred between the 2014-15 seasonal influenza vaccine and circulating H3N2 viruses that had undergone antigenic drift, the interagency working group developed an action plan that may mitigate future occurrences of such an event. HHS has taken a series of steps to increase the probability that a late season change to tri-or quadrivalent vaccine

could be made or that a supplemental monovalent vaccine could be produced, if warranted. In June 2015, ASPR hosted a meeting with vaccine manufacturers, international public health partners, and HHS representatives to solicit opinions on HHS recommendations and plans to address potential seasonal influenza vaccine mismatches due to viral antigenic drift. Several proposed actions by HHS for immediate implementation included the following:

- 1) Work with the WHO to expand influenza strain surveillance capacity that ensures greater and earlier detection of emerging influenza viruses globally that may have drifted antigenically, thereby, informing decisions on generating more vaccine viruses sooner.
- 2) If antigenic drift is identified after the WHO and FDA's VRBPAC make their seasonal vaccine strain recommendations in February or early March, CDC and FDA will apprise HHS senior leadership, and together with WHO, will notify the manufacturers. In addition, FDA will notify the Chair of VRBPAC. This formalizes the previous communication practices.
- 3) If there is evidence of antigenic drift, CDC will provide candidate vaccine viruses (for egg and cell-based vaccines) that are antigenically similar to the drifted strain and provide the new candidate vaccine viruses to the manufacturers for production testing.
- 4) In the event of suspected antigenic drift, FDA will develop matched vaccine potency reagents for the new candidate vaccine viruses and make them available to manufacturers.

These and other steps have been tested and will be further refined based on a tabletop exercise that was conducted on November 10, 2015, with HHS agencies and vaccine manufacturers as

individual participants, to solicit their individual opinions. The exercise outcome is expected to inform an HHS action plan for rapid development and manufacturing of a revised trivalent or quadrivalent seasonal influenza vaccine or a supplemental monovalent vaccine. The FRMM leadership also recommended to HHS leadership additional action items to implement over the immediate, interim, and long-term horizons (18 months – five years) to address vaccine mismatch issues in the areas of virus surveillance and characterization, technologies, vaccine design, and vaccine distribution. Together with the influenza vaccine manufacturers, federal agencies, WHO and its collaborating laboratories, and regulatory authorities and public health leadership in other countries, a coordinated action plan may be adopted to address antigenic drift and vaccine mismatch problems.

Progress in Influenza Vaccine Manufacturing

In spite of the difficulties inherent in preparing influenza vaccines, we continue to make progress in our preparedness efforts in collaboration with BARDA, CDC, NIH, and other stakeholders. For example, FDA has licensed numerous new influenza vaccines over the past decade, including cell-based influenza vaccines, recombinant protein vaccines, and quadrivalent influenza vaccines. Cell-based and recombinant protein influenza vaccines provide an alternative to the traditional egg-based process of manufacturing, and provide the potential for a faster start-up of the vaccine manufacturing process. FDA licensed the first cell-based influenza vaccine, Flucelvax, manufactured by Novartis, in November 2012, and the first recombinant influenza vaccine, FluBlok, manufactured by Protein Sciences, in January 2013. In addition, FDA has licensed quadrivalent influenza vaccines from four different manufacturers since 2011. Prior to the licensure of quadrivalent vaccines, all FDA-licensed vaccines were intended to

protect against two influenza A strains and one influenza B strain. The quadrivalent vaccines are intended to protect against two influenza A strains and two influenza B strains, representing the two B lineages that often are co-circulating in any given season. To enhance pandemic preparedness, in 2013, FDA licensed an adjuvanted H5N1 vaccine, manufactured by GlaxoSmithKline Biologicals, and has worked with U.S. Government partners and manufacturers to facilitate the development of candidate vaccines directed at H7N9 avian influenza A.

Surveillance efforts are more extensive than ever before and offer the potential for early detection of emerging influenza viruses. The number of candidate vaccine virus strains available to manufacturers has increased greatly over the last few years, providing them with more options to increase vaccine yields. FDA, in conjunction with BARDA, CDC, and NIH, continues efforts to develop high-yield candidate vaccine strains, as well as more modern, faster methods to measure vaccine potency and sterility. To further address the challenges presented by the constantly changing nature of influenza viruses, scientists in government laboratories, academic institutions, and vaccine manufacturers are working to develop new-generation vaccines that might be longer-lasting and provide broader protection against drifted strains. Although these vaccine development efforts are still in early stages, some may have the potential to increase and broaden protection against influenza. FDA will continue to work with U.S. Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines and identify methods that have the potential to speed the manufacturing process for existing vaccines. Our goal is to better protect the American public, including those at higher risk of complications from influenza.