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STATEMENT

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"FDA's Role in Preventing Influenza and Protecting the American Public Through Vaccination"

BEFORE THE

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INTRODUCTION

Mr. Chairman 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. 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. Minor changes in the protein structure in influenza viruses, known as "antigenic drift," occur frequently, enabling the virus to cause repetitive influenza outbreaks by evading immune recognition. These changes also have the potential to decrease the effectiveness of the vaccines targeting these protein structures. Major changes, known as "antigenic shift," can also occur and have the potential to lead to a pandemic, as we experienced in 2009. 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 in the vaccine 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 the WHO's Collaborating Centers for Influenza—which includes the Centers for Disease Control and Prevention (CDC), the WHO Essential Regulatory Laboratories, which includes 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 to determine how well antibodies induced by these vaccines react to recently isolated viruses. These Essential Regulatory Laboratories are located in national regulatory agencies and have a critical role at the global level for developing, regulating and standardizing influenza vaccines, working closely with WHO and industry. 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 late 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, usually within a couple of weeks of 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.

Once the strains are selected, candidate influenza viruses that are adapted for high growth are generated and accepted by WHO collaborating centers. The candidate influenza viruses are provided to the licensed vaccine manufacturers to generate the "seed viruses" for manufacturing their influenza vaccines. 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. This influenza season, more than 150 million doses were manufactured. 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 biennial facility inspections.

2014-2015 Influenza Season

Influenza viruses are constantly changing, and variants can appear at any time, including during the vaccine manufacturing period. There is always the possibility of a less-than-optimal match between the influenza virus strains that end up predominating in the influenza season and those covered by the vaccine. This occurred in the current influenza season.

Since September, most of the influenza A (H3N2) viruses found in patients with influenza in the United States are different (drifted) from the H3N2 vaccine virus component, suggesting that the vaccine's ability to protect against the drifted virus will be reduced. At the time the strain selection recommendation was made in late February 2014, the majority of cases of influenza disease were caused by influenza A (H1N1), not influenza A (H3N2), and the drifted H3N2 viruses had not been detected in the United States. These drifted H3N2 viruses were not detected until March 8, 2014, and were uncommon. Since that time, the drifted H3N2 viruses gradually increased as a proportion of H3N2 viruses isolated over the ensuing months and have

caused a majority of influenza cases this season. WHO made its recommendations for the 2015 Southern Hemisphere influenza vaccine on September 25, 2014, by which time these drifted H3N2 viruses were common, prompting a recommended change in the upcoming Southern Hemisphere vaccine composition. At this point, because of the time required to manufacture influenza vaccine, it would not have been possible to make adequate amounts of influenza vaccine containing the drifted H3N2 virus in time for our peak influenza season, which usually occurs between December and February.

This situation stands in contrast to the emergence of pandemic H1N1 virus in the spring of 2009. By May 2009, the pandemic virus had spread rapidly throughout the world, resulting in thousands of cases in the United States, and WHO had made a candidate vaccine recommendation. WHO declared an influenza pandemic on June 11, 2009. Although tremendous efforts toward manufacturing of H1N1 pandemic vaccines began in the spring, it was not until late October 2009 that the first doses of this vaccine became available, with the bulk of the supply becoming available only in the December to January time frame. Although the production of a supplemental H1N1 vaccine in 2009 demonstrated flexibility to adapt to rapidly changing circumstances, the time required for manufacturing, testing, release, and distribution of the vaccine could only be compressed so much. As described in more detail in the next section, since 2009, significant advances have been made to broaden influenza vaccine manufacturing approaches in an effort to further compress timelines.

Even when a drifted virus appears later in the year, as it has done the current season, vaccination is still important to prevent disease and minimize the public health burden of influenza.

Influenza vaccines contain three or four influenza viruses (depending on whether the vaccine is a trivalent or quadrivalent formulation), so that even when there is a less than ideal match or lower effectiveness against one virus, the vaccine may protect against the other viruses.

Progress in Influenza Vaccine Manufacturing

In spite of the difficulties inherent in preparing influenza vaccines, we have made progress in our preparedness efforts in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), CDC, NIH, and other stakeholders. For example, new influenza vaccines have been licensed since 2009, 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 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 influenza.

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 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.