TESTIMONY

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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

"EXAMINING U.S. PUBLIC HEALTH PREPAREDNESS FOR AND RESPONSE EFFORTS TO SEASONAL INFLUENZA"

MARCH 8, 2018

RELEASE ONLY UPON DELIVERY

Introduction

Chairman Harper, Ranking Member DeGette, distinguished members of the Subcommittee, I am Dr. Scott Gottlieb, Commissioner of the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to be here today to discuss FDA's role in the highly collaborative effort in preventing influenza through vaccination in the United States.

Influenza (flu) is a major public health concern. Annually, flu causes illness in a substantial proportion of the U.S. population and may result in serious complications, including events leading to hospitalization and death. Influenza viruses are highly unpredictable. Each year, they can present new challenges for vaccine manufacturers, public health agencies, providers, and patients. The current flu season has been especially challenging, with widespread activity that has affected all fifty states, resulting in a record number of hospitalizations.

Although healthcare providers are still busy taking care of people with influenza this season, essential work has started on the production of next year's influenza vaccines. As this process moves forward, FDA is committed to continuing to examine the factors that impacted vaccine effectiveness from this season. Our goal is to work with other public health agencies to ensure that vaccines produced for the next season will have the greatest chance of being effective in preventing influenza.

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 the predominant circulating viruses anticipated 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).

A Global Process for Virus Strain Selection

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 technical meetings. To identify virus strains likely to cause illness during the upcoming influenza season, experts from WHO Collaborating Centers for Influenza (which include the Centers for Disease Control and Prevention (CDC)), the WHO Essential Regulatory Laboratories (this includes FDA's Center for Biologics Evaluation and Research (CBER)), and other influenza and public health experts study recently circulating influenza viruses 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 then reviewed 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. This is to accommodate the time that is 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 U.S., 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 meeting to provide recommendations on strain selection for the upcoming 2018-2019 United States influenza season took place on March 1, 2018.

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. CDC and other WHO Collaborating Centers provide most of the information considered in the course of this review. 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.

Influenza viruses that grow well in culture, 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. No other routine vaccine is produced, FDA-approved, and distributed every year across the United States within an approximately six-month time frame. The manufacturing timelines are tight and the process of producing influenza vaccines 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 an update to the strains included in each licensed flu vaccine, there is limited flexibility in the timelines for influenza vaccine production and availability. There is the possibility that advances in manufacturing, as well as the adoption of different technologies for the production of antigen, can help compress this process and provide greater predictability. Certain technologies could also offer more opportunity to adjust the vaccine closer to the influenza season should a new influenza strain emerge after production has already begun.

Vaccine manufacturers must annually submit to FDA a supplement to their license to include the updated influenza virus antigens in their vaccine. FDA must review and approve a supplement before the updated version of the influenza vaccine containing new virus antigens can be distributed. Manufacturing of each antigen to be included in the vaccines occurs sequentially over several months, usually from December (produced at risk by manufacturers before the strain recommendations are made) until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents that 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.

2017-2018 Influenza Season

FDA's VRBPAC met on March 9, 2017, to provide recommendations on the composition of the influenza vaccine for the 2017-2018 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 2016-2017 vaccines, and the availability of candidate strains and reagents. The Committee recommended that the trivalent

influenza vaccines for the U.S. 2017-2018 influenza season be produced with the following: an A/Michigan/45/2015 (H1N1) pdm09-like virus, an A/Hong Kong /4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus (B/Victoria lineage). The Committee also recommended that quadrivalent influenza vaccines be produced with the above three strains and the following additional B strain: a B/Phuket/3073/2013-like virus (B/Yamagata lineage).

This year, much of the influenza-related illness has been caused by one strain of influenza A called H3N2, with another strain of influenza A called H1N1 and strains of influenza B contributing to lesser extents. CDC recently published the interim estimates of 2017-2018 seasonal influenza vaccine effectiveness in the United States. Overall adjusted vaccine effectiveness for H1N1 and influenza B strains was not too far off from prior seasons at 67 percent and 42 percent, respectively. However, overall adjusted effectiveness for H3N2 influenza was only 25 percent. The effectiveness of the vaccine against H3N2 in children 6 months to 8 years of age was 51 percent, yet the effectiveness in those 65 years and older was only 17 percent. Individuals over 65 years of age always tend to have a lower response rate to influenza vaccine, and improving the response in this age group is one of the challenges that we must address.

Reduced effectiveness of vaccination against H3N2 relative to H1N1 and influenza B has been seen in prior seasons. Scientists at FDA are working with colleagues at other agencies to try to understand the reasons for the difference in the effectiveness of the vaccine against H3N2 relative to the other types of influenza. The work that they are doing includes laboratory and epidemiologic investigation. For example, in trying to understand whether one type of influenza vaccine performs better than another in individuals 65 years of age and older, they are making use of an established collaboration with the Centers for Medicare and Medicaid Services (CMS).

As part of this collaboration, our scientists are looking at the effectiveness of various influenza vaccines in preventing hospitalizations for influenza and treatment for influenza-like illness in four million individuals for whom information is available in the large database regarding what type of influenza vaccine they received. They are using the database to look for differences in effectiveness in those receiving egg-based and cell-based vaccines, as well as differences in effectiveness in those who were vaccinated with standard-dose versus high-dose influenza vaccine and adjuvanted influenza vaccine. The high dose vaccine contains four times as much of the influenza antigen as standard vaccines, and the adjuvanted influenza vaccine contains an ingredient meant to boost the immune system's response to the vaccine. Differences observed in the effectiveness of differently-produced vaccines against H3N2 may offer important insights into why the most widely-used, egg-based vaccines have reduced efficacy against this strain.

Progress in Influenza Vaccine Manufacturing

Despite difficulties inherent in preparing influenza vaccines, we continue to make progress in our preparedness efforts in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), CDC, the National Institutes of Health (NIH), and other stakeholders.

New influenza vaccines have been licensed in recent years, including cell-based influenza vaccines, recombinant protein vaccines, and quadrivalent influenza vaccines. Cell-based and recombinant protein influenza vaccines provide alternatives to the traditional egg-based process of manufacturing, and provide the potential for a faster vaccine manufacturing process. FDA has licensed a cell-based influenza vaccine and a recombinant influenza vaccine. FDA has also licensed quadrivalent vaccines that are intended to protect against two influenza A strains (H3N2 and H1N1) and two influenza B strains. In addition, FDA has approved high-dose and adjuvanted vaccines specifically for the elderly population who can require an adjuvant or higher exposure to antigen in order to develop an adequate immune response to the influenza vaccine.

CDC's surveillance efforts to monitor for circulating influenza strains are more extensive than ever before. These efforts 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 NIH, BARDA, and CDC, 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. Ultimately, developing a universal influenza vaccine that provides protection against many different strains of flu from year-to-year would be ideal.

However, the reality of such a vaccine is likely to still be many years away. In the meantime, FDA is collaborating with Federal partners and with industry to improve the manufacturing of the current generation of influenza vaccines. Advances in manufacturing, including wider consideration of cell-based manufacturing, continuous manufacturing, and the use of recombinant vaccines, may offer the best near-term opportunity to improve vaccine timeliness and effectiveness. Our scientists are interested in looking at whether advanced manufacturing technologies, including continuous manufacturing of cell-based and recombinant vaccines, could help facilitate much more agile response to changes in influenza strains. Use of continuous manufacturing could also have the added benefit of allowing the rapid scale-up and production of vaccine in the United States within compact manufacturing facilities. The potential benefits of these advancements are also applicable to our ongoing efforts to enhance our nation's preparedness for pandemic influenza.

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 such as the very young and the elderly.

Diagnostics and Antivirals

Finally, I want to highlight FDA's role in approving rapid diagnostic tests and antiviral therapies. Currently, there are 13 rapid flu tests available for marketing in the U.S. These rapid flu tests, which are medical devices, include antigen-based tests and nucleic acid-based tests that are available for use in primary care. To improve the overall accuracy and reliability of flu testing, FDA recently reclassified antigen-based rapid influenza diagnostic tests, which included new performance and testing requirements to demonstrate the ability of a rapid flu test to detect currently circulating viruses. We expect the new requirements to lower the number of misdiagnosed flu infections by promoting the development of new, improved tests that can more reliably detect the virus. This will ensure patients and providers are receiving accurate diagnostic information without reducing access to reliable tests.

Currently there are several antiviral drugs approved for prophylaxis and/or for treatment of acute uncomplicated influenza, and several others in clinical trials. FDA monitors for shortage, safety, and manufacturing issues associated with the available drugs. FDA works closely with developers of antiviral drugs to review and advise on development pathways and clinical trial designs to enhance understanding of the role of these drugs in influenza preparedness and treatment. A major goal is to encourage availability of a variety of treatments that can be shown to benefit a broader range of patient populations and influenza outbreak strains.

Conclusion

In closing, I would like to assure the Committee that FDA will continue to advance policies and the science to help improve the overall reliability, efficiency, and effectiveness of the vaccine production process. We will apply all the knowledge gained in conjunction with NIH, BARDA, CDC, and other Federal partners as we work together with manufacturers to ensure that the best possible vaccines are available next season to protect against the flu.