

TESTIMONY

OF

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U.S. FOOD AND DRUG ADMINISTRATION

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Introduction

Chair DeGette, Ranking Member Guthrie, distinguished members of the Subcommittee, I am Dr. Peter Marks, director of the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to describe FDA's efforts in close coordination and collaboration with its Federal partners inside and outside of the U.S. Department of Health and Human Services to ensure the development, approval, and availability of critical safe and effective medical products to address seasonal and pandemic influenza.

These products include drugs, such as antiviral agents for the prevention and treatment of influenza; biologics, including vaccines for the prevention of influenza across the age spectrum; and devices, both for the rapid and the definitive diagnosis of influenza, as well as for supportive medical care.

FDA's role in helping to foster development, approval, and availability of safe and effective medical products

FDA involvement in these products spans the entire product lifecycle. The Agency provides scientific and regulatory advice to industry, researchers and other stakeholders across the product development spectrum, from the time prior to any formal regulatory submission is made for a product, and throughout development under FDA's investigational new drug or device exemption process.

FDA makes use of all available regulatory tools and expedited programs, including those provided by Congress, as appropriate, to help advance products critical for public health through development to approval. These programs may provide expedited timelines for review and

increased interactions between the Agency and sponsors. Americans can rely on the fact that, when it approves a medical product, FDA has determined that it is safe and effective. This confidence in a product's safety and effectiveness can be particularly important in combatting increased vaccine hesitancy, which is threatening to undermine the public health benefits of vaccination.

Following approval, the Agency uses real world data to monitor the safety of these products through both passive and active post-market surveillance. Passive surveillance involves the submission of adverse event reports by patients, providers, and manufacturers to the FDA. FDA also performs active post-market surveillance of drugs and biologics through various databases, including FDA's Sentinel system. For some of the products, such as influenza vaccine, the Agency also uses large databases in the post-market setting to evaluate vaccine effectiveness. FDA has helped validate this methodology for determination of effectiveness by comparing the results from conventional clinical trials of high dose versus standard dose seasonal influenza vaccines with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database. This collaboration has provided valuable analysis in support of public health.

FDA also works with manufacturers of approved products to help ensure continued supply and availability of critical medical products. The Agency does this by promptly reviewing proposed technical or manufacturing changes and ensuring the continued quality of these products. In addition, FDA has several programs in place to help promote and evaluate emerging technologies that, if adopted, could result in more efficient and agile manufacturing of critical products such as the influenza vaccine. Finally, should a shortage of a medical product occur,

FDA actively works with manufacturers and other U.S. Federal agencies to address supply issues for the product in shortage.

Composition of influenza vaccines

Influenza viruses continually undergo changes in their genetic makeup. These changes can occur from one season to the next; they can also occur during an influenza season. Unlike other vaccines, the composition of influenza vaccines must be updated annually so that they are effective against the predominant circulating viruses anticipated in the upcoming influenza (or commonly known as “flu”) season. The strains of virus used in vaccine production this year 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, the recently-circulating influenza viruses and recent global disease patterns are studied by 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. 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. 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 process, which is repeated in various other countries across the globe, 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. As described below, FDA takes WHO's recommendations into account as it selects strains for the upcoming influenza season.

FDA's Role in Virus Strain Selection 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. Each year, in considering the WHO recommendations, FDA brings together public health and

influenza disease experts to recommend which influenza virus strains should be included in that year's 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 to select the strains for the vaccine to be used in the Northern Hemisphere in the upcoming year. In addition to reviewing the WHO recommendations, the committee also reviews information regarding influenza virus strains that have caused human illness in the previous year, how these viruses are changing, and disease trends. The strain selection meetings for the current 2019-2020 United States influenza season took place on March 6 and March 22, 2019.

Following strain selection, influenza viruses that 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.

For the 2019-2020 season, there have been more than 160 million doses of influenza vaccine produced for use in the United States, and manufacturing demands for influenza vaccines are substantial. No other vaccine is produced, FDA-approved, and distributed every year across the nation within an approximately six-month time frame. The manufacturing timelines are tight and 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 to update each licensed influenza vaccine, there is limited flexibility in the timelines for production and availability.

Manufacturing of each antigen to be included in the vaccines occurs sequentially over several months, usually from December, when it is 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 distribution in the United States.

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, as warranted, to ensure compliance with current good manufacturing practice requirements. The rigorous timelines currently required for vaccine production, including strain selection, reagent preparation, manufacturing of vaccine components, and formulation, fill, and distribution of the final product, leave little room for error or for changes in vaccine composition after the initial strain selection process.

Collaboration across the Federal government is essential to meeting these challenges, and FDA looks forward to continuing to work with its Federal partners to help address the public health threat caused by seasonal and pandemic influenza. In September 2019, in recognition of the limitations noted above and the importance of cross-agency collaboration, the President

signed the *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health*. Broadly, the Executive Order directs the Biomedical Advanced Research and Development Authority (BARDA), CDC, the National Institutes of Health (NIH), and FDA to accelerate the adoption of improved influenza vaccine technologies.

On the horizon are advances in manufacturing, as well as the adoption of different technologies for production of antigen, that could help compress the timeline for this production process and provide greater predictability. Certain technologies could also offer more opportunity to adjust the composition of the vaccine closer in time to the influenza season, should a new influenza strain emerge after production has already begun. FDA is supporting the development of such technologies through internal work and collaborations with external researchers, with the end goal of more efficient and agile manufacturing of influenza vaccines.

FDA's Role in Influenza Vaccine Research

In addition to our important role in helping to foster vaccine development and in conducting our evaluation to determine influenza vaccine safety and effectiveness, FDA also has critical applied research functions. For example, the Agency's laboratories produce reagents crucial for influenza vaccine production. FDA is one of four WHO essential reference laboratories producing these critical reagents, including candidate viruses and potency reagents for vaccine manufacturers in both the Northern and Southern Hemispheres.

FDA also conducts applied scientific research to address current challenges in seasonal and pandemic influenza vaccine production, such as improving their effectiveness and enhancing the ability to adjust rapidly to emerging strains of influenza.

FDA scientists are collaborating with others to develop the needed advanced manufacturing technologies to more efficiently produce influenza virus or influenza antigen. The development and adoption of advanced manufacturing technologies has the potential to address the need for maximally efficient, agile and flexible manufacture of both current and next-generation influenza vaccines.

As noted by others at today's hearing, the key here is being able to produce large amounts of vaccine effective against an emerging influenza strain in a very timely manner. Producing such a vaccine against a pandemic or new seasonal influenza strain more efficiently must be done while also maintaining FDA's high standards for safety and effectiveness on which the American public relies.

Conclusion

As we continue to invest in the future of manufacturing and vaccine technology, we also need to remember the importance of simply ensuring that more people are vaccinated with available vaccines each flu season. And we also must work hard to ensure that products used to treat influenza – including antivirals and IV saline – are available, and that we take steps to prevent and address shortages.

As always, FDA remains committed to communicating and sharing updates with the public about all aspects of our flu response. I look forward to answering your questions today.

Thank you.