DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

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"Influenza: Perspective on Current Season and Update on Preparedness"

BEFORE THE

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

February 13, 2013

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Jesse Goodman, Chief Scientist at the Food and Drug Administration (FDA or the Agency). I am also a practicing Infectious Diseases physician. Thank you for the opportunity to be here today with my colleague from the Centers for Disease Control and Prevention (CDC) to discuss FDA's role, working with partners throughout government and the private sector, in protecting the public from influenza—one of the most serious infectious disease threats to our nation.

Flu seasons are unpredictable and this year's H3N2 seasonal flu epidemic is a telling reminder of the continuing challenge of influenza and the need for individuals worldwide to take seasonal influenza very seriously. Seasonal influenza causes substantial illness and death, not only posing high risk to the elderly, but also to pregnant women, infants, and children. While influenza remains a major challenge in ways I will touch on later, our nation has made tremendous progress in preparedness for seasonal and pandemic flu, particularly since the 2009 H1N1 pandemic.

FDA's overall responsibility, with respect to influenza, is helping to ensure that medical countermeasures (MCM) used to diagnose, prevent, and treat influenza—including drugs, vaccines, and diagnostic tests—are safe, effective, and secure. FDA also works with manufacturers and other stakeholders in their efforts to enhance the development and availability of new products to fulfill unmet public health needs, including the application of regulatory science to improve the diagnosis, prevention, and treatment of influenza. In meeting the challenge of flu, and in preparing for and responding to other infectious disease threats, including

the threat of bioterrorism, FDA works closely with its partners within the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE),[1] as well as with manufacturers and global regulatory and public health partners.

In responding to this year's influenza epidemic, FDA has been working closely with CDC, industry, and other stakeholders to make as much vaccine as possible available to the public in a timely way and to enhance the supplies of needed diagnostics and antivirals to help diagnose and treat those who do get influenza. FDA has approved and lot-released all available influenza vaccine from six manufacturers, who collectively produced more than 140 million doses for the United States—far more than was available only a few years ago. This vaccine is well-matched to the circulating virus causing most influenza disease this year.

Although some regions of the country have experienced spot shortages of flu vaccine, this is due to increased public attention and high demand brought on by a flu season that arrived early and forcefully. In addition to doing all that is possible to facilitate access to vaccine, FDA is working closely with CDC and other agencies and offices within our mutual parent agency, the Department of Health and Human Services (HHS), and manufacturers to monitor and help address potential shortages. For example, faced with a shortage of the antiviral, liquid Tamiflu (oseltamivir), for young children, FDA worked with CDC and the manufacturer to provide information to pharmacists to safely prepare liquid Tamiflu from Tamiflu capsules. Further, FDA has exercised regulatory flexibility with respect to the rapid release of 2 million Tamiflu

[1]This includes FDA, the National Institutes of Health (NIH), CDC, the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), the Department of Defense (DoD), the Department of Homeland Security, the Department of Veterans Affairs, and the Department of Agriculture.

capsules that had been held in reserve. FDA also has generated data to show that properly stockpiled Tamiflu supplies can remain usable for up to 10 years beyond their date of manufacture and has made public health authorities aware that FDA will exercise enforcement discretion with respect to use of these stockpiled reserves, if they are needed.

As the current influenza outbreak spread, FDA anticipated a proliferation in the promotion of fraudulent products for prevention and treatment. FDA significantly increased its surveillance of online promotions for unapproved flu products, which come in a variety of forms, including supplements, conventional foods, and unapproved drugs and devices. Of particular concern are products promoted as alternatives to the flu vaccine and unapproved antiviral drugs sold by illegitimate online pharmacies. FDA considers the promotion of unapproved products to prevent or treat the flu to be a potentially significant threat to public health, and responsible firms may be subject to regulatory and enforcement actions. FDA also has issued a "Beware of Fraudulent Flu Products" article to alert consumers about fraudulent flu products and "Red Flag" promotional claims to watch out for.

FDA's Role in the Development of Vaccines to Prevent Influenza

FDA does not make vaccines; however, each and every year we play a unique and critical role in facilitating influenza vaccine production and availability. Preparing for each year's influenza season is an intensive, time-critical, and highly orchestrated and collaborative effort involving FDA, CDC, the World Health Organization (WHO), vaccine manufacturers, and the public health community. It is a year-round process that requires worldwide influenza surveillance, selection of virus strains, preparation of antigens and reagents for vaccine manufacturing, approval of each year's vaccines as a strain change supplement to their licenses, and the testing,

lot release, and distribution of over 100 million doses of vaccine, followed by continual safety monitoring.

Influenza is a very challenging virus in that its surface proteins change constantly to evade both our immune systems and vaccines. As a result of these changes, in most years, at least one of the strains in the vaccine must be changed to keep up with changes in the circulating virus. Over 100 million doses of vaccine must be manufactured each year for the United States in a short period of time; almost every year it is a somewhat different vaccine and can present unique manufacturing challenges. Since the virus is so unpredictable, and vaccine production is complex, FDA must be continuously alert and adaptable.

The U.S.-licensed seasonal influenza vaccines currently in use are made based on representative strains of three (trivalent) influenza viruses—two influenza A strains (H1N1 and H3N2) and one B strain, or more recently, the quadrivalent vaccine that includes an additional B strain and will be available beginning next flu season. These are selected to protect against the strains that, based on worldwide surveillance, are likely to cause the most human infection during the upcoming season. FDA selects the appropriate strains with input from our Vaccines and Related Biological Products Advisory Committee and relies on a global disease surveillance effort led by WHO. CDC is a major participant in this surveillance effort.

Currently available influenza vaccines contain either purified hemagglutinin (HA), a surface protein of the influenza virus against which the human body directs much of its immune response, or a live version of a highly weakened, modified influenza virus. These vaccines, neither of which can cause flu, are referred to as inactivated or live-attenuated influenza

vaccines, respectively. Influenza vaccines have a proven safety record over many years of use in hundreds of millions of individuals annually; serious adverse events are very rare.

The effectiveness of influenza vaccines is lower than that for other vaccines and lower than we would prefer from a public health perspective. Their effectiveness, however, is still significant and, when well-matched to circulating strains, they are effective at protecting the majority of those vaccinated. CDC's preliminary estimate for this year is that vaccinated individuals had 60 percent fewer cases of confirmed influenza than did unvaccinated individuals. Influenza vaccine is most effective in healthy young people and typically less effective in the elderly, particularly those who have chronic diseases and whose immune systems may not typically respond well to either influenza or influenza vaccines. However, given their high risk of complications from influenza disease, vaccination is still highly recommended for the elderly. Live-attenuated influenza vaccine is indicated for healthy individuals, ages 2 to 49.

An important point to emphasize is that symptoms suggesting influenza can be caused by multiple other viruses as well as bacteria, and the majority of respiratory illnesses, particularly mild ones, are not due to influenza. Thus, it is not surprising for individuals to receive the flu vaccine and still get a seemingly flu-like respiratory illness. While influenza vaccines cannot prevent these other infections and the current vaccines cannot completely protect everyone from influenza, they are still our safest and most effective measure to prevent this life-threatening disease. Thus, CDC recommends that nearly all people over 6 months of age receive flu vaccine.

Vaccine Production

Each year, FDA begins working with manufacturers at the earliest stages of vaccine development and continues to interact with them throughout production. After strain selection, which

typically occurs each February, the reference influenza viruses are sent from a WHO Collaborating Center to the licensed vaccine manufacturers to generate "seed virus" banks used to produce the vaccines. FDA develops and calibrates "reference reagents," which are provided to vaccine manufacturers and to our regulatory counterparts throughout the world. These reagents are essential to test the inactivated vaccines for potency and to formulate standard dosages. FDA evaluates each strain of inactivated virus and the manufacturers then formulate the bulk vaccines. Manufacturers submit samples to FDA for testing along with results of their own testing. FDA reviews this information and conducts its own testing prior to releasing any formulated bulk vaccine lots. Manufacturers then fill and finish the vaccines into vials and syringes, or, for live-attenuated vaccine, into nasal sprayers. Manufacturers exhaustively test their influenza vaccines, including for potency, purity, and sterility, prior to distribution. The process of lot release and vaccine distribution continues through the fall and early winter. This influenza season, FDA released all lots of influenza vaccine by early December. Egg-based vaccines typically require about six months for complete vaccine production each season.

Efforts to Increase Influenza Vaccine Manufacturing Capacity and Supply

Ten years ago, there were only three U.S.-licensed influenza vaccine manufacturers. In 2004, significant manufacturing difficulties with one manufacturer resulted in limited supplies. To better insure against future problems, FDA initiated significant efforts to increase both the diversity and amount of the vaccine supply and to upgrade manufacturing oversight and quality industry-wide.

From 2004-2007, working with the Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), HHS

and major manufacturers of influenza vaccine throughout the world, we achieved a doubling of the number of U.S.-licensed manufacturers (from three to six—on January 16, 2013, we approved a seventh) and an approximate doubling of vaccine manufacturing capacity and supply. FDA accomplished this by stimulating interest in production for the U.S. market and by utilizing an accelerated approval pathway to speed the evaluation and licensure of new influenza vaccines.

Recent Developments in Influenza Vaccine Production

As a result of substantial ASPR/BARDA investment and intense interactions with FDA, two novel influenza vaccines made with alternative manufacturing technologies were approved recently. These vaccines will supplement the supply of seasonal vaccines, and the new technologies offer the potential for faster start up of vaccine manufacturing for future pandemic threats.

Flucelvax, approved in November 2012, is the first U.S.-licensed flu vaccine manufactured using cell-culture technology instead of fertilized chicken eggs. Potential advantages of cell-culture technology include: (1) elimination, through use of well-characterized and readily available cells, of the need for large numbers of fertile eggs (which could be threatened, for example, by an avian flu outbreak); (2) the potential for manufacturing influenza vaccine using strains of virus that do not grow well in eggs; and (3) the potential for faster start-up and scale-up of manufacturing in the event of a pandemic. Currently, the cell-based Flucelvax vaccine is manufactured by Novartis in Germany, but they plan to eventually move production to the cell-based facility in Holly Springs, North Carolina, built with ASPR/BARDA support and extensive FDA technical assistance. This facility significantly increases both overall and U.S.-based manufacturing and capacity.

Flublok, manufactured by Protein Sciences Corporation (PSC) and also developed with support from ASPR/BARDA and NIH, was approved in January 2013. It is the first U.S.-licensed flu vaccine manufactured using recombinant DNA technology. Flublok also does not require eggs, nor is it necessary for PSC to have the influenza virus available to begin production of Flublok. Flublok's novel manufacturing technology uses an insect virus grown in insect cells to produce the HA protein subsequently used to produce the influenza vaccine. It can be manufactured simply based on the HA genetic sequence of any desired flu virus, something that can be obtained and verified within days. This affords a potential significant advantage over previously licensed technologies in an emergency because the production of reference virus strains, which can be a significant time-limiting factor in responding to a pandemic or other outbreak, is not needed. Recombinant and molecular DNA expression technologies, including those being supported by ASPR/BARDA, have started to allow approaches that do not depend on virus growth to be used for production of influenza vaccines, and these technologies could serve as platforms for production of other vaccines as well.

FDA also has worked with BARDA to retrofit manufacturing facilities to increase existing domestic egg-based flu vaccine production surge capacity. These successes in developing increased domestic production capacity and novel non-egg-based production techniques are particularly important in enhancing readiness to rapidly produce large amounts of vaccine in response to an emerging pandemic. To this end, FDA is collaborating with ASPR/BARDA to provide technical assistance to BARDA-funded Centers for Innovation in Advanced Development and Manufacturing (ADM). These Centers were established specifically to increase U.S. domestic vaccine surge production capacity in response to a pandemic or other

emerging threat and offer a new model for public-private partnerships, bringing together small biotech companies, academic institutions, and large experienced pharmaceutical companies. Production sites include those in Texas, North Carolina, and Maryland, and will use modern technologies for accelerating production, improving quality, and expanding domestic vaccine manufacturing capabilities.

FDA is working closely with ASPR/BARDA and the ADM sites to provide technical advice to facilitate high-quality development and manufacturing and, ultimately, regulatory approval. Similarly, FDA has provided expertise to the Department of Defense's ADM programs and to the Defense Advanced Research Projects Agency (DARPA) in their efforts to rapidly manufacture plant-based influenza vaccines.

In addition to helping us better prepare for influenza pandemics, these new production approaches and facilities will increase our nation's agility and capacity to respond to other, unanticipated infectious disease threats, natural or man-made.

Process Improvements Through Regulatory Science

In addition to enhancing vaccine production and U.S.-based capacity, with the support of Congress, and as highlighted in Secretary Sebelius' 2010 Medical Countermeasure Review, FDA has significantly expanded its infrastructure to support increased capacity for rapid testing and lot release of influenza vaccines and for targeted regulatory science. For example, the Agency developed a technique for rapid sterility testing that provides results almost three times faster than previous assays. To facilitate adoption of these new rapid sterility methods, FDA amended its regulation regarding sterility testing to provide more flexibility while ensuring continued

safety. Further, FDA is collaborating with HHS, CDC, and NIH to develop new potency tests and more rapid ways to make potency reagents, which would help make both seasonal and pandemic influenza vaccines available more quickly. Taken together, all of these approaches are helping to safely reduce the time needed to produce a vaccine and make it available.

Improved Influenza Vaccines

While all of these efforts have better prepared us for both seasonal influenza and future pandemics, we also need more effective flu vaccines. This is a high priority across the PHEMCE. Although HHS funding and programmatic activities in this area are largely directed by NIH and ASPR/BARDA, given the importance of such efforts, I will briefly mention them here. An ideal influenza vaccine would be effective in preventing flu after a single dose, even in individuals with weakened immune systems who are most at risk, such as the elderly and those with chronic diseases. It would provide strong immunity that lasts beyond a single season and protects not just against the strains of flu the vaccine is based on, but against the altered strains of flu that continuously evolve. Ideally, it could also afford at least some protection against markedly different flu viruses that arise and have major pandemic potential. When needed, large amounts of such a vaccine could be produced rapidly.

While we currently do not have vaccine candidates with all of these characteristics, there are a number of promising approaches under active research and development supported by the U.S. Government and/or by industry. These include use of novel adjuvants—substances added to a vaccine that can boost the immune response of the individual. Some adjuvanted candidate vaccines appear to stimulate a much stronger immune response, including against H5 avian influenza for which existing flu vaccines only stimulate a weak response. Novel adjuvants also appear potentially able to stimulate a broader immune response, e.g., a response that works better

than current vaccines against viruses that have changed from the strain included in the vaccine. Many studies are still under way regarding adjuvanted vaccines and their potential for influenza, including studies at FDA's Center for Biologics Evaluation and Research concerning both adjuvant effects on the immune response and on safety. Novel adjuvants have been stockpiled with ASPR/BARDA support, in case they are needed for a severe pandemic.

Other novel approaches which may improve the immune response to flu vaccines include the use of virus proteins packaged in virus-like particles, a type of approach already used in licensed vaccines to prevent cervical cancer. Also, approaches using DNA-based vaccines, or use of DNA and protein vaccines in sequence, may enhance the immune response and provide novel approaches to rapid vaccine production. In addition to these novel approaches to enhance immunity through new vaccine technologies, NIH, ASPR/BARDA, and industry are supporting efforts to make vaccines using parts of the virus that do not change as much from strain to strain, including well-conserved parts of the HA gene and a number of other genes. These approaches are often grouped together as "universal flu vaccines" for the potential they may offer to protect against multiple flu strains. FDA is working with innovators to facilitate development of such products.

Vaccine Safety Monitoring

Robust safety monitoring is critical, both to ensure the continued safety of vaccines and to maintain public confidence. FDA monitors influenza vaccine post-licensure and reviews, interprets, and analyzes adverse event reports collected through the Vaccine Adverse Event Reporting System (VAERS). In collaboration with the Centers for Medicare and Medicaid Services (CMS), FDA conducts near real-time monitoring for Guillain-Barre Syndrome (GBS), a rare adverse event of high interest because of its unexpected association with swine flu vaccine

in 1976. In addition, FDA collaborates with CDC to perform studies and rapid-cycle analysis as needed through CDC's Vaccine Safety Datalink (VSD), an active surveillance system with nine health maintenance organizations. During the 2009 H1N1 pandemic, FDA, in collaboration with CDC, DoD, Department of Veterans Affairs, CMS, and regulatory counterparts around the world, implemented aggressive, near real-time safety monitoring, including for GBS, with rapid-cycle analysis of numerous data sources. This allowed active detection and follow-up of any potential safety signals and was instrumental in addressing potential concerns as they arose. To further enhance safety surveillance, FDA is developing the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, the largest electronic real-time active surveillance system for vaccine safety in the United States.

Development and Review of Tests to Diagnose Influenza

Given that so many different infections can present similarly to influenza, accurate, sensitive, and convenient diagnostic tests for influenza are important. Accurate diagnosis is critical to treating influenza effectively. Accurate diagnosis also limits unneeded use of antivirals and antibiotics, conserves needed drugs, and reduces the risk of resistance. Enhancing the availability, performance and use of influenza diagnostics is the subject of considerable interest across the PHEMCE. The lessons learned from the 2009 pandemic were transformative. FDA made 18 tests available under Emergency Use Authorizations, strengthening interactions with manufacturers and collaborations with CDC and other federal partners. In addition, these stakeholders continue to work together to fill critical gaps, such as the need for appropriate specimens for manufacturers to validate their diagnostic tests.

FDA also has been working with CDC, HHS, and manufacturers to help improve the sensitivity of rapid influenza tests, including the ability to better adapt to the changing influenza strains that

circulate each season. This collaboration has led to comparison testing studies of devices and CDC guidance to inform physicians how to best use and interpret these tests.

FDA continues to work with manufacturers to facilitate research and development and to review and approve new influenza diagnostic tests. This includes work to help stimulate the development of highly multiplexed tests to simultaneously detect multiple types of organisms, including influenza virus, in order to accurately diagnose the specific cause of a patient's disease. Congress' support of the MCM initiative has been important to these efforts.

In November 2012, FDA published a draft guidance document for the validation of highly multiplexed tests and is now using newly developed scientific/regulatory processes for reviewing submissions for highly multiplexed tests. Since the 2009 pandemic emergency was terminated, FDA has cleared a total of 16 new influenza tests, four of which were rapid tests.

Development of Antivirals to Treat Influenza

Antiviral drugs are used to treat people with flu to reduce the severity and duration of disease. There are four FDA-approved antivirals, including two currently being used to treat (or, in certain circumstances, to prevent) seasonal influenza: Tamiflu and Relenza (zanamivir). FDA works closely with its HHS partners, including NIH and ASPR/BARDA and the manufacturers, to monitor and review information relevant to the effectiveness, safety, and availability of antivirals in order to enhance their use. In December 2012, FDA approved oseltamivir dosing for use in children between 2 weeks and 1 year of age, making it the first influenza antiviral approved for children younger than 1 year old. In addition, FDA has worked to assess the stability of these drugs, helping to improve the information base for their inclusion in the U.S. Strategic National Stockpile, which serves as an emergency back up for commercial supplies.

FDA is conducting research to evaluate how varying shipping and storage conditions affect antiviral drugs, which will inform future stockpiling decisions.

FDA also recognizes the need for new and improved influenza drugs, including intravenous drugs, to address, for example, drug resistance and treatment needs for severe illnesses. The development of these products is challenging and complex. To help product developers, FDA released a guidance document entitled "Influenza: Developing Drugs for Treatment and/or Prophylaxis" in 2011. In addition, the Agency works closely with innovators to provide feedback on proposed development plans and clinical trial designs.

When individual patients are seriously ill and the treating clinicians believe there is a need to use antiviral drugs that are still under development (e.g., intravenous formulations), FDA works with treating clinicians and manufacturers to facilitate access to drugs under expanded-access processes, if there is an unmet need that requires use of the investigational drug outside of the existing clinical trials. It is important to note that providing expanded access on an individual basis generally does not provide reliable information about treatment effects. Controlled clinical trials are important for overall assessment of the risks and benefits of new antivirals. They do not always show the benefits that had been hoped for, based on preliminary information. Even trials with less-than-hoped-for outcomes can be a source of learning to improve the approach to future drug development.

CONCLUSION

FDA plays a key role, working closely with our government partners and with industry, in facilitating the development, evaluation, and availability of safe and effective measures to diagnosis, treat, and prevent influenza. We have come a long way in enhancing our ability to

prepare for and respond to both seasonal and pandemic influenza, and we are fully engaged in an ongoing and intensive effort to further enhance our nation's preparedness and response. The response to influenza is, year after year, a public-private partnership.

I want to note how important the capacity and engagement of our public health and health care systems are for detecting and responding to major events for influenza and other threats. For influenza, a strong surveillance system can help improve the odds that the vaccine produced each year will be effective, and, even more important, help detect earlier the emergence of a pandemic. A coordinated response, with public health, health care organizations, industry, and government working together, much like we saw in the response to the 2009 pandemic, is what we need to protect our nation against these threats.

FDA's MCM Initiative, supported by Congress, has helped us play an active engaged role in public health preparedness and response, supporting highly interactive relationships. We are much better prepared, have achieved several recent landmark developments and product approvals, and developed new science that promises a bright future. We are all working together and I am optimistic that the gains that have been made are on track to continue.

Thank you, again, for the opportunity to testify on this issue. I welcome your input and questions.