Addressing Pandemic Influenza Preparedness

SLIDE 1
This presentation will discuss pandemic influenza preparedness. This presentation is now a summary of historical events that were unfolding at the time the presentation was originally given in October of 2009.

SLIDE 2
This presentation will briefly cover background information on pandemic flu and specific facts with respect to the 2009 H1N1 pandemic; how the FDA responded to that H1N1 pandemic, including activities specific to the Center for Biologics Evaluation and Research, known as CBER.

The discussion will cover the licensure of H1N1 vaccines, as well as the regulatory pathways for pandemic vaccine licensure, and then very briefly touch on emergency use authorization.

SLIDE 3
Historically there have been three major pandemics: the emergence of H1N1 in 1918, the emergence of H2N2 in 1957, and the emergence of H3N2 in 1968. The World Health Organization, known as WHO, has defined three criteria for a pandemic outbreak. A pandemic virus has a novel influenza hemagglutinin subtype to which the general population has little or no immunity. A pandemic virus must also cause significant morbidity and mortality, and efficiently transmit from human to human.

Since April 21, 2009, when the U.S. Centers for Disease Control and Prevention, or CDC, released their first morbidity and mortality weekly report, "Dispatch" on two U.S. cases of the newly-emergent 2009 H1N1, the numbers steadily increased over time. This prompted the WHO to declare a pandemic phase 6, on June 11, 2009.

SLIDE 4
Some facts about the newly-emergent 2009 H1N1: Index cases were from a 10-year-old boy in San Diego County, and a 9-year-old girl from Imperial County, California. It's important to note that there was no epidemiological link between the two cases, as they were over 200 miles apart; that there were no known exposures to zoonotic risk factors; that the virus isolates were genetically related; that they were triple reassortants, of human, swine and avian genes; and that they were also antigenically similar. The current landscape seen for this 2009 H1N1 as of September 27, 2009, is there were over 343,000 confirmed cases globally, and over 4,000 deaths with the case fatality ratio of approximately 1.2.

At that time, it was the predominantly circulating strain in the Southern Hemisphere, and it was also anticipated to be the predominant strain in the Northern Hemisphere in the subsequent season. The WHO had their Southern Hemisphere Strain Selection Meeting in the fall of 2009, and recommended that the newly emergent 2009 H1N1 be incorporated into the subsequent seasonal flu vaccine for the Southern Hemisphere.

In the fall of 2009, widespread circulation of this H1N1 Strain in the United States was anticipated.

From preliminary surveillance reports provided by the CDC,it was found that 26 out of 50 U.S. states were reporting widespread influenza activity. The proportion of outpatient visits for influenza-like illness was above the national baseline, although the number of deaths attributable to pneumonia and influenza at the time fell below the epidemic threshold.

SLIDE 5

What was done to prepare for all of this? All of the pandemic preparedness efforts were tested in real life by H1N1. Everything from the development of a national strategy for pandemic influenza, to the various implementation plans and continuity of operations plans, to a pre-pandemic "tabletop," or mock exercise, and other functional exercises which were completed.

SLIDE 6

Specifically what did the FDA do to respond to this outbreak? An H1N1 Task Force was established on April 24, 2009, which was comprised of teams that encompassed center-specific and cross-cutting disciplines. An FDA Emergency Operations Center was activated, and an incident management like approach was implemented and coordinated from the highest levels in the Commissioner's office. There were frequent teleconferences, two times daily for approximately the first 2 weeks, with daily situational reports, and then about once a week with weekly situational reports.

In May 2009, an FDA liaison was deployed to CDC headquarters to facilitate coordination between FDA and CDC.

SLIDE 7

Various center-specific teams were established and are listed on the slide. As you can see, there were quite a few teams that were spread across the FDA medical product centers, including the Center for Drugs Evaluation and Research and the Center for Devices and Radiological Health. You will see that the teams from CBER consisted of a Vaccine and a Blood team.

FDA also had Teams from the Office of Regulatory Affairs, which is FDA's inspectorate component. The Center for Food Safety and Nutrition, and the Center for Veterinary Medicine also were part of the team.

SLIDE 8

FDA also had quite a few cross-functional teams that were led from the Commissioner's office with participation from the various medical product centers. These cross-functional teams dealt mainly with agency cross-cutting issues. One notable team was the legal team, who worked very closely with the Centers on the issuance of emergency use authorizations, which this talk will touch upon later. Some emergency use authorizations were, most notably, two for FDA approved drugs, Tamiflu and Relenza for unapproved uses, as well as RT-PCR H1N1 diagnostic kits and disposable N95 respirators.

SLIDE 9

The CBER Blood and Vaccine Teams were responsible for briefing FDA leadership on various subjects ranging from blood safety and supply status of reference strains and reagents; status of vaccine manufacturing; the development and the conduct of clinical trials that would help guide the use of the 2009 H1N1 vaccine; and efforts to develop, qualify and validate, if possible, the appropriate serological assays in order to evaluate the clinical trial specimens meaningfully to inform decision making.

SLIDE 10

Let's focus a little bit more on what CBER specifically did with respect to vaccine development.

First, regardless of whether or not it is H1N1, CBER has always played a central role in influenza vaccine development on a yearly basis, because CBER is a WHO Essential Regulatory Laboratory, or ERL. That means that CBER participates in the yearly strain selection, receives the isolates from the CDC and from different countries, and runs serological assays to look at the antigenic characterization of these viruses and determine whether or not these viruses are antigenic variants. Then, the data are presented to the WHO, which informs WHO decision-making on whether or not these variants are different enough to require a change in the vaccine strain in the upcoming seasonal flu vaccine.

CBER works very collaboratively with the CDC. CBER works to generate high-growth reassortants that are suitable for vaccine production. CBER produces, calibrates, cross-calibrates, and provides potency reagents for SRID testing. CBER works with the manufacturers to do antigenic confirmation of the seed viruses to be used in vaccine production. And, associated with this, CBER does lot release and a range of confirmatory testing.

SLIDE 11

In addition to all of these activities, which are done on a routine annual basis, CBER also was greatly immersed in H1N1-specific activities. This slide outlines some of what took place. CBER held weekly meetings with manufacturers of U.S. licensed seasonal influenza vaccine. These meetings were facilitated by the

Biomedical Medical Advanced Research and Development Authority, or BARDA, at the Department of Health and Human Services. These meetings generally discussed the status of H1N1 vaccine development, production, and regulatory pathway to licensure.

CBER held weekly meetings with the National Institutes of Health and BARDA regarding the design, implementation, and conduct of the clinical trials. These meetings were intended to help guide in the eventual use recommendations of these H1N1 vaccines once they became available.

CBER held weekly meetings with the CDC and state health departments regarding fall vaccine plans. The participants in these meetings were all at the state level, representing the people who managed the state distribution plans to get the vaccine to the end user.

SLIDE 12

The FDA had numerous collaborations with international entities, collaborations with the European Medicines Agency, or EMA, with Health Canada, and with the Therapeutic Goods Administration, or TGA, regarding the sharing of H1N1 clinical trial designs and data.

These interactions were conducted under our Agency confidentiality arrangements with these individual regulatory bodies. There was very intense collaboration with the WHO and other international health authorities regarding pharmacovigilance activities, including the sharing of case definitions and background rates for adverse events of special interest.

SLIDE 13

The U.S. government, namely BARDA, worked with U.S. licensed manufacturers for seasonal influenza vaccine with the intent to purchase H1N1 vaccines for the U.S. population as outlined in the U.S.'s National Strategy for Pandemic Influenza. On September 15, 2009, the influenza A-H1N1 2009 monovalent vaccines were licensed from Sanofi Pasteur, Novartis, CSL, and MedImmune. These were licensed through a strain-change supplement to their existing seasonal influenza vaccine licenses.

What is meant by strain-change supplement? Licensed manufacturers have had years and years of experience with strain-change supplements, because they do this every year with the seasonal vaccine. The H1N1 vaccine was no different. First, the 2009 H1N1 was identified and provided to the manufacturers as a reference virus. The reference strain then went through the same process of vaccine development as is routinely done for the seasonal influenza vaccines. The only difference was that the vaccine was not a typical annual Trivalent vaccine, but rather a monovalent vaccine. The 2009 H1N1 vaccines were not novel. They were produced and released according to the same license processes as their seasonal counterparts. It is also important to note that prior to

any licensing action that FDA took, FDA publicly discussed its approach with several federal advisory committees, including CBER's own Vaccines and Related Biological Products Advisory Committee, the ver-pac. The FDA also discussed the vaccine candidates with the National Vaccines Advisory Committee, the en-vac, and many other advisory committees. FDA's approach to licensing the H1N1 vaccine, using the seasonal influenza vaccine pathway, was again discussed with many international regulators. FDA sought to be as transparent as possible, so the rest of the world would know what FDA planned to do with this H1N1 vaccine.

These vaccines are not novel. They were produced and released via the same license processes. After licensure, BARDA directed the manufacturers to ship the vaccines directly to CDC-managed distribution sites. The vaccines were federally distributed by CDC based on pro rata allocation to the states. Vaccine availability to the end user was based on state-managed plans. The CDC's Advisory Committee on Immunization Practices, or ACIP, issued recommendations for use over the course of the availability of the vaccine, from limited quantities to much larger scales. Initially, recommendations for target priority groups were made until the vaccine's availability ramped up.

SLIDE 14

Just a little bit about the regulatory options for pandemic flu vaccines. Regarding data for the support of licensure of pandemic influenza vaccines, refer to the guidance entitled "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines." To fully understand this guidance, however, one must be aware of the distinction between pandemic vaccines and pre-pandemic vaccines, because these terms have been used very widely and very differently across the globe.

According to one definition, a "pandemic" vaccine is one that is not made until a pandemic has been declared. The vaccine is made against an actual circulating pandemic strain. A pre-pandemic vaccine is any vaccine that is produced against a virus of pandemic potential, during a time where there is no declared pandemic. However, in the FDA guidance, pandemic and pre-pandemic are applied to a given vaccine according to its indications for use. That is, a pandemic vaccine is one seeking an indication for use for the active immunization of persons at high risk of contracting influenza by the subtype contained in the vaccine. The subtype could be changed out in any given year via the strain change supplement describe earlier. Such a vaccine can be used during a pandemic, be used in initial waves prior to an available exact strain match, or be used in a pre-pandemic scenario for individuals at increased risk of exposure, such as military or CDC personnel being deployed to high-risk areas.

SLIDE 15

The reference FDA guidance does not address vaccines seeking a pre-pandemic indication. This indication has yet to be defined, but considerations may include

the use of vaccine during low pandemic threat levels and may consider population priming strategies. This particular guidance is directed toward the pandemic influenza vaccines, that is, vaccines seeking a pandemic indication. If a manufacturer holds a U.S. license for a seasonal influenza vaccine, whether inactivated or live-attenuated, and intends to use the same licensed manufacturing process to produce the pandemic influenza vaccine, the FDA guidance states that the safety follow-up for a pandemic vaccine will be at least 6 months post-vaccination and that the size of the safety database must be agreed upon by CBER.

It is also important to note that a careful immunogenicity assessment is needed most typically in the form of a dose-ranging study to determine the appropriate dose to inform formulation decisions. For manufacturers who do not have a U.S. licensed seasonal vaccine, the approval of a pandemic vaccine can be requested through the accelerated approval pathway. An adequate pre-licensure safety and immunogenicity database would be required. These specific requirements would need to be predetermined between the sponsor and the FDA, during the product-development process. After licensure, there would be a regulatory requirement for the demonstration of clinical benefit.

SLIDE 16

Regarding emergency use authorization, the Secretary of Health and Human Services has delegated authority to the FDA Commissioner the ability to authorize the use of an unapproved medical product, or the use of an approved medical product for an unapproved indication during a declared emergency justifying its use if all of the legal criteria are met. The mechanism FDA uses to take this step is known as an Emergency Use Authorization, or EUA. The issuance of an EUA is based on the circumstances of the emergency and the totality of the scientific information. The Commissioner may authorize such emergency use upon a request by a sponsor, if there is information from adequate and well-controlled clinical trials that there is reason to believe that the medical product may be effective; that the known and potential benefits outweigh the known and potential risks; and that there is no adequate, approved, and available alternative to the product that is being considered for emergency use. The EUA is product-specific, and remains in effect for 1 year, unless revoked, terminated or renewed.

Emergency Use Authorization is not a pathway to licensure, nor can data generated under an EUA be used as a basis for licensure. This is because the regulations require that licensure must be based on adequate, well-controlled trials, which presumably would not be the case in an emergency with a product used under an EUA.

SLIDE 17

The last slide shows references to find some of the relevant guidance for CBER's pandemic preparedness activities and policies, as discussed in this presentation.

SLIDE 18

This concludes the presentation, "Addressing Pandemic Influenza Preparedness".

We would like to acknowledge those who contributed to its development. Thank you.