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Licensure of Pandemic Influenza Vaccines: Demonstration of Effectiveness

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Licensure of Pandemic Influenza Vaccines: Demonstration of Effectiveness

1.0 Introduction

A cornerstone of pandemic influenza prevention is the development and timely availability of a vaccine which is well matched to the pandemic influenza strain. The most expeditious path to licensure of such a vaccine is as a "strain change supplement" to an already licensed vaccine, this is the process used for the annual seasonal influenza vaccine strain change and used to license the Influenza A (H1N1) 2009 Monovalent Vaccines. To enable timely licensure as a "strain change supplement" it is essential that influenza vaccines against influenza A subtypes of pandemic potential are licensed prior to the onset of the pandemic in question. In the event of a pandemic, or when a pandemic is imminent, prior licensure of such prototype influenza vaccines will shorten the time to licensure of a vaccine against the pandemic strain as a "strain change supplement."

An application for licensure of a pandemic vaccine must include chemistry, manufacturing and controls information and data to support the safety and effectiveness of the vaccine. Clinical studies conducted with a prototype pandemic influenza vaccine prior to a pandemic can provide immunogenicity data to establish the dose and vaccination regimen[1], as well as safety data.[2] However, for vaccines against influenza A subtypes of pandemic potential that are not included in the seasonal influenza vaccines (i.e., other than H1 and H3), clinical endpoint efficacy studies are not feasible in the absence of circulation of the pandemic strain. Furthermore, it may not be ethical or feasible for vaccine manufacturers to conduct a clinical endpoint efficacy study during a pandemic, as evidenced by the 2009 influenza A H1N1 pandemic. FDA is working with manufacturers interested in developing pandemic influenza vaccines to establish pathways to support effectiveness prior to licensure. The approaches outlined in this document are specifically tailored to pandemic influenza vaccines for which it is not feasible for manufacturers to conduct clinical endpoint efficacy studies; the approaches are not applicable to other vaccines. The specific scenarios outlined pertain to hemagglutinin (HA) based adjuvanted and unadjuvanted pandemic influenza vaccines.

The subject of discussion at this advisory committee meeting is pathways to licensure of pandemic influenza vaccines, with particular emphasis on types of data that can be used to support effectiveness of such vaccines prior to licensure.

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[1] Clinical studies with live attenuated influenza pandemic vaccines performed in advance of a pandemic influenza outbreak present special circumstances with regard to data needed to support dose and regimen as well as with regard to shedding and transmission of the vaccine strain. These considerations are discussed in CBER's Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, 2007, but are not addressed in this briefing document.

[2] Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, 2007

2.0 Background:

2.1 Influenza pandemics

Three influenza pandemics occurred in the twentieth century (1918, 1957, and 1968). Influenza viruses, especially highly pathogenic influenza strains like H5N1, which is endemic in wild birds in many parts of the world and continues to infect people sporadically, remain a pandemic threat. Between 2003 and January 2012, the World Health Organization (WHO) has reported 583 confirmed human cases of H5N1 infection, and almost 60 percent of those infections have been fatal.[3]

In April 2009, a novel influenza A virus, a reassortant of avian, swine, and human influenza viruses, was detected in California. This novel 2009 H1N1 influenza virus was subsequently found to be the same one causing an expanding outbreak of late season respiratory illness in Mexico. On June 11, 2009, WHO declared a global pandemic, making 2009 H1N1 the first influenza pandemic in over 40 years. Unlike seasonal influenza viruses, the 2009 H1N1 influenza virus continued to circulate throughout the summer months in the Northern Hemisphere, and caused a second larger wave of disease in the fall.

In the U.S., five Influenza A H1N1 (2009) Monovalent Virus Vaccines were licensed in the fall of 2009. These vaccines were considered strain changes to licensed seasonal influenza vaccines, as described in Section 3.1.

While the threat of the 2009 influenza A H1N1 pandemic has subsided, the risk of another pandemic has not diminished. Influenza A virus pandemics may be caused by circulation of a novel influenza virus of subtypes included in the seasonal vaccine (e.g. swine origin H1N1 or H3N2) or circulation and efficient transmission of Influenza A subtypes not previously associated with respiratory disease in humans (e.g. H5, H7, H9). For preparedness planning it is essential to have a path to licensure for vaccines containing any Influenza A subtype of pandemic potential.

2.2 U.S.-licensed influenza vaccines

There are currently six manufacturers of seasonal influenza vaccines licensed in the U.S. In 2009, FDA licensed five Influenza A (H1N1) 2009 vaccines as strain changes to licensed seasonal influenza vaccines as summarized in Section 3. 1 of this document. One unadjuvanted pandemic influenza vaccine against Influenza A (H5N1) has been licensed in the U.S. as summarized in Section 3.2 of this document. There are currently no U.S.-licensed adjuvanted seasonal or pandemic influenza vaccines although several are in advanced clinical development.

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[3] Cumulative Number of Confirmed Human Cases of Avian Influenza A/ (H5N1) Reported to WHO, 2003-2012. Available online: http://www.who.int/influenza/human_animal_interface/EN_GIP_20120124CumulativeNumberH5N1cases.pdf Accessed January 24, 2011.

3.0 Influenza vaccines against subtypes of pandemic potential made by manufacturers of U.S.-licensed seasonal influenza vaccines: Demonstration of effectiveness

This section addresses pandemic influenza vaccines made by manufacturers of U.S.-licensed seasonal influenza vaccines. The following scenarios are addressed:

- Pandemic vaccine against an Influenza A virus subtype included in a licensed seasonal vaccine, manufactured using the same process (section 3.1)

- Pandemic vaccine against an Influenza A virus subtype not included in a licensed seasonal vaccine, manufactured using the same process (section 3.2.1)

- Pandemic vaccine against an Influenza A virus subtype not included in a licensed seasonal vaccine, manufactured using the same process except that the pandemic vaccine contains an adjuvant (section 3.2.2)

3.1 Pandemic vaccines against influenza A virus subtypes included in licensed seasonal influenza vaccines (e.g. swine origin H1N1 and H3N2)

The pandemic (H1N1) 2009 virus consisted of an influenza A subtype contained in currently licensed seasonal trivalent influenza vaccines. In July 2009, FDA presented the approach to licensure for these vaccines to the VRBPAC for discussion. The VRBPAC supported FDA's approach to license the Influenza A (H1N1) 2009 Monovalent Virus Vaccines as strain change supplements to a manufacturer's seasonal influenza vaccine license. Each monovalent vaccine contained the same quantity of HA as a single strain of the seasonal vaccine and was approved for use in the same population as the respective seasonal vaccine. Consistent with seasonal influenza vaccine strain changes, clinical safety and immunogenicity data were not required for the inactivated unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccines. Limited clinical safety data were provided at the time of licensure of the pandemic Influenza A (H1N1) 2009 live virus vaccine to verify attenuation of the vaccine strain. Safety and effectiveness of each Influenza A (H1N1) 2009 Monovalent Virus Vaccine was inferred from data included in the approved seasonal influenza vaccine license application. Although each manufacturer conducted clinical studies with their Influenza A (H1N1) 2009 Monovalent Virus Vaccine to verify the dose and regimen, these data were not required for approval of the strain change supplement.

The strain change approach to license the Influenza A (H1N1) 2009 Monovalent Virus Vaccines was feasible because the seasonal influenza vaccine included the influenza A H1N1 subtype and there was clinical experience showing that the dose and dosing regimen for Influenza A subtypes included in the seasonal vaccine were safe and effective. This approach is not applicable to vaccines containing Influenza A subtypes not included in the seasonal influenza vaccine or containing an adjuvant. In these cases licensure of a prototype pandemic vaccine first would be required to permit a strain change supplement (see section 3.2).

Summary: Unadjuvanted influenza A H1 and H3 subtype virus vaccines manufactured according to the same process as the manufacturer's U.S.-licensed seasonal vaccine are licensed as strain change supplements to the approved seasonal influenza vaccine without a requirement for clinical data at the time of licensure.

3.2 Pandemic vaccines against influenza A virus subtypes not included in a licensed seasonal influenza vaccine (e.g. H5 and H7)

3.2.1 Pandemic vaccines against Influenza A virus subtypes not included in a licensed seasonal vaccine, but manufactured using to the same process

In April 2007, CBER licensed a monovalent H5N1 vaccine (Influenza Virus Vaccine, H5N1) manufactured by Sanofi Pasteur Inc. for use in persons 18 through 64 years of age who are at increased risk of exposure to the H5N1 influenza virus subtype included in the vaccine. This vaccine is included in the Strategic National Stockpile. This vaccine was discussed by the VRBPAC in February 2007, and the committee recommended that the available data were sufficient to support safety and effectiveness of the product. Safety and immunogenicity data supported the dose of antigen (90 ug/1 mL dose) and dosing regimen (2 doses approximately 28 days apart) in persons 18 through 64 years of age. The vaccine is manufactured by the same process as the seasonal influenza vaccine manufactured by Sanofi Pasteur, Inc. (Fluzone) which is approved for use in persons 6 months of age and older. Implicit in the approval of the H5N1 vaccine was that effectiveness data for Fluzone support that of the H5N1 vaccine.

Summary: An Influenza A subtype vaccine against an influenza A subtype not included in the manufacturer's U.S.-licensed seasonal vaccine, that is manufactured according to the same process, would be licensed as a new vaccine. Safety and immunogenicity data to select the dose and dosing regimen are required prior to licensure. The effectiveness of the manufacturer's licensed seasonal influenza vaccine supports the effectiveness of the new subtype.

3.2.2 Pandemic vaccines against Influenza A virus subtypes not included in a licensed seasonal vaccine, but manufactured using the same process except that the pandemic vaccine contains an adjuvant

Some pandemic influenza vaccines under development contain a novel adjuvant to enhance immunogenicity, achieve dose sparing and/or to provide cross protection against related strains. For these adjuvanted vaccines, immunogenicity and safety data accrued in the population for which licensure is sought will define the HA dose, adjuvant content and dosing regimen. Endpoints for evaluation of immunogenicity are discussed in CBER's Guidance for Industry on clinical evaluation of pandemic influenza vaccines.[2]

Currently, all adjuvanted pandemic influenza A subtype vaccines in advanced development are manufactured according to the same process as a seasonal influenza vaccine (with the exception of the addition of adjuvant in the pandemic vaccine).

The corresponding licensed seasonal influenza vaccines can be placed into one of two regulatory categories:

> Category 1 (Traditional Approval). The effectiveness of the corresponding U.S.-licensed seasonal influenza vaccine has been confirmed in a clinical endpoint efficacy trial(s).
>
> Category 2 (Accelerated Approval). The effectiveness of the corresponding U.S.-licensed seasonal influenza vaccine is based on immunogenicity endpoints reasonably likely to predict clinical benefit, but the clinical benefit has not been verified yet. The seasonal influenza vaccine was approved under the Accelerated Approval regulations (21 CFR 601.41) and studies to verify the clinical benefit are ongoing..

For an adjuvanted pandemic influenza vaccine against an influenza A subtype not included in the seasonal influenza vaccines, but that is manufactured according to the same process as a licensed seasonal influenza vaccine (with the exception of the adjuvant), safety and immunogenicity data to support the dose and dosing regimen are required prior to licensure.

If the corresponding licensed seasonal influenza vaccine was approved under the Traditional Approval pathway on the basis of a clinical endpoint efficacy trial(s) (Category 1, above), then effectiveness of the new subtype (e.g., H5) vaccine is inferred from the effectiveness of the manufacturer's licensed seasonal influenza vaccine.

If the corresponding licensed seasonal influenza vaccine was approved under the Accelerated Approval Regulations, based on immunogenicity data, with verification of clinical benefit pending (Category 2 above), there are two potential pathways to licensure of the adjuvanted pandemic influenza vaccine:

a) The adjuvanted influenza A subtype vaccine (e.g. H5) is approved under the accelerated approval regulations, with a requirement to verify clinical benefit using the licensed seasonal influenza vaccine.
b) Effectiveness of the adjuvanted influenza A subtype vaccine (e.g. H5) is inferred from effectiveness data (such as from a case-control study) using an unlicensed adjuvanted pandemic influenza A H1N1 subtype vaccine made by the same process.

4.0 Pandemic influenza vaccines against subtypes of pandemic potential manufactured by a process not licensed in the U.S.: demonstration of effectiveness

As described in CBER's Guidance for Industry on clinical evaluation of pandemic influenza vaccines[2] , the Accelerated Approval pathway is available for pandemic vaccines manufactured by a process that is not licensed in the U.S.. If manufacturers of such vaccines also develop a seasonal influenza vaccine, a clinical endpoint efficacy study with the licensed seasonal vaccine can fulfill the requirement to verify the clinical benefit of the pandemic vaccine (as described above in section 3.2).

If a manufacturer of a pandemic influenza vaccine does not pursue U.S. licensure of a seasonal influenza vaccine, other approaches to demonstrating effectiveness may be possible. CBER would like the advisory committee to discuss potential alternate pathways to demonstrate effectiveness of a prototype pandemic influenza vaccine prior to a pandemic.

5.0 Summary

A critical component of pandemic planning is licensure of prototype pandemic influenza vaccines. Manufacturers are developing such vaccines; licensure of the prototype vaccine will permit approval of pandemic influenza vaccines of the same hemagglutinin A subtype as "strain change supplements" in the event of a pandemic. Pre-licensure safety and immunogenicity data in the target age groups will be required to support the HA dose, adjuvant dose (if used) and dosing regimen. However, it is not feasible for manufacturers to conduct clinical endpoint efficacy studies to evaluate protection against disease caused by influenza A subtypes of pandemic potential not included in seasonal vaccines (i.e. other than H1 and H3) because these non-seasonal subtypes (e.g. H5) are not currently circulating among humans.

For manufacturers of U.S.-licensed seasonal influenza vaccines the clinical endpoint effectiveness data accrued with the seasonal influenza vaccine can support the effectiveness of influenza A subtype (e.g. H5) unadjuvanted and adjuvanted pandemic vaccines made by the same process. Alternatively, clinical endpoint effectiveness data accrued with a non-U.S.-licensed adjuvanted influenza vaccine can support effectiveness of an influenza A subtype (e.g. H5) adjuvanted pandemic vaccine made by the same process. These pathways to demonstrate effectiveness are only available to pandemic influenza vaccines for which it is not feasible for manufacturers to conduct clinical endpoint efficacy studies and do not apply to other vaccines.

After licensure and in the event of a pandemic, manufacturers are expected to work with the FDA and other governmental agencies on plans to collect safety and effectiveness data, such as through epidemiological studies.