FDA Briefing Document
Vaccines and Related Biological Products Advisory Committee Meeting
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Highly Pathogenic Avian Influenza (H5)
Virus Vaccines

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1. 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 via a "strain change supplement" to an already licensed vaccine, a process used for the annual seasonal influenza vaccine strain change also used to license the pandemic 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 a pandemic (hereafter the term "pandemic" is intended to include nonseasonal influenza virus outbreaks or epidemics associated with a public health emergency declaration). 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 via a "strain change supplement."

An application for licensure of a pandemic vaccine must include chemistry, manufacturing and controls information and substantial evidence 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 current 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 influenza A subtype. 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 has worked with manufacturers interested in developing pandemic influenza vaccines to establish pathways to support effectiveness prior to licensure and these approaches have been described previously (Ref: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines | FDA and Briefing Document, November 14-15, 2012 VRBPAC).

As part of highly pathogenic avian influenza (HPAI) virus pandemic preparedness, including considerations for updating the composition of prototype influenza A (H5) monovalent vaccines, FDA is requesting that VRBPAC discuss and provide input on a proposed strain change process and expected data requirements for updating licensed prototype pandemic influenza vaccines during the inter-pandemic period (see Section 5).

[1] Clinical studies with live attenuated pandemic influenza 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. Background

2.1 Influenza pandemics

Three influenza pandemics occurred in the twentieth century (1918, 1957, and 1968) and one so far in the twenty-first century (2009). Influenza viruses remain a pandemic threat, especially HPAI virus subtypes like H5N1, which is endemic in wild birds in many parts of the world and continues to infect people sporadically. Since 2020, a variant of the A/goose/Guangdong/1/96-lineage of H5N1 avian influenza viruses belonging to the H5 clade 2.3.4.4b, has led to an unprecedented number of deaths in wild birds and poultry in many countries in Africa, Asia, and Europe. In 2021, this H5 virus spread to North America, and in 2022, to Central and South America.[3]

HPAI A(H5N1) viruses of clade 2.3.4.4b (hereafter referred to as H5 clade 2.3.4.4b viruses) first gained attention in 2014 due to an extensive capacity for reassortment and spread. Although initially outbreaks were mainly restricted to wild and domestic birds, H5 clade 2.3.4.4b viruses have subsequently displayed an increased capability to infect mammalian species. Near the end of 2021 and early 2022, H5 clade 2.3.4.4b viruses entered North America, and subsequently the United States, spreading rapidly and causing large outbreaks in both wild aquatic birds, commercial poultry, and dairy cows. Detection of these viruses in birds across five continents, and subsequent spillover to mammals (including humans) raised global public health concerns about H5 clade 2.3.4.4b viruses. Outbreaks were reported in farmed mink in Spain, New England harbor and grey seals in the U.S., sea lions in Peru and Chile, and cats in France and Poland. These outbreaks suggested that H5 clade 2.3.4.4 viruses were evolving for more efficient mammalian transmission, an attribute previously not associated with HPAI influenza A(H5N1) viruses. This has been supported by recent reports of 14 human cases in the U.S. since March 2024 following exposure to contaminated environments or animals infected with H5 clade 2.3.4.4b viruses.[4]

The last time the World Health Organization (WHO) declared a global influenza pandemic was 15 years ago on June 11, 2009, making 2009 H1N1 (swine influenza) the first influenza pandemic in over 30 years. On August 10, 2010, WHO declared an end to the global 2009 H1N1 influenza pandemic; however, (H1N1) pdm09 virus continues to circulate as a seasonal flu virus, and while not at pandemic levels, causes illness, hospitalization, and deaths worldwide every year. Although the pandemic potential of (H1N1) pdm09 virus has diminished, the risk of another potential global influenza pandemic has not. 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, and H9). Illustrative of this potential threat, candidate vaccine viruses (CVVs) for influenza viruses with pandemic potential are regularly prepared by the World Health Organization (WHO) Collaborating Centers and Essential Regulatory Labs. Generation of these vaccine reagents is an essential component of the overall global strategy for influenza pandemic preparedness and the WHO currently have

[3] Avian influenza A(H5N1) virus. Available online: https://www.who.int/teams/global-influenza-programme/avian-influenza/avian-a-h5n1-virus Accessed September 25, 2024.

[4] H5 Bird Flu: Current Situation. Available online: H5 Bird Flu: Current Situation | Bird Flu | CDC Accessed September 25, 2024

CVVs available for several strains of H5, H7, H9, H10, and H1v and H3v (swine influenza A) viruses. CVVs prepared from H5 clade 2.3.4.4b viruses include A/Astrakhan/3212/2020 and A/American Wigeon/South Carolina/22-000345-001/2021. Additional relevant background information can be found in the WHO statement on *Genetic and antigenic characteristics of clade 2.3.4.4b A(H5N1) viruses identified in dairy cattle in the United States of America* (see WHO Statement May 2024) and the WHO statement on *Genetic and antigenic characteristics of zoonotic influenza A viruses and development of candidate vaccine viruses for pandemic preparedness* (see WHO Statement September 2024).

While the risk of infection with HPAI H5 clade 2.3.4.4b viruses, currently circulating in Europe, is considered low for the general population, the risk for occupationally or otherwise exposed groups to avian influenza-infected birds or mammals is assessed as low-to-moderate by the European Centre for Disease Prevention and Control. That said, starting in June 2024 Finland offered preemptive bird flu vaccination to some workers with exposure to animals.[5] Finland procured Seqirus A/Astrakhan/3212/2020 (H5N8)-like strain with MF59 adjuvant vaccines for 10,000 people, each consisting of two injections (i.e., 20,000 doses), as part of a joint European Union procurement of up to 40 million doses for 15 nations. To date, no other EU countries have offered preemptive bird flu vaccination.

2.2 Current HPAI H5 clade 2.3.4.4b cases

H5 clade 2.3.4.4b viruses are widespread in wild birds worldwide and are causing outbreaks in poultry and U.S. dairy cows, with several recent human cases in U.S. dairy and poultry workers. While the current public health risk is low, CDC continues to assess the situation carefully and is working with state governments to monitor people with animal exposures. CDC is also using its influenza surveillance systems to monitor for H5 bird flu activity in people. Since March 24, 2024, there have been 14 confirmed human cases in the U.S.

There have been 4 cases following exposure to dairy cows.[6] The cases were from Texas (1 case), Michigan (2 cases), and Colorado (1 case). All four cases were mild with primarily conjunctivitis (eye symptoms), received oseltamivir treatment, and recovered uneventfully.

There have been 9 cases following exposure to poultry[7] reported across two facilities in Colorado with HPAI A (H5N1) detections in poultry culling operations. All reported conjunctivitis, half reported headaches, body aches, and fever or chills, and a third reported cough and shortness of breath. All were treated with oseltamivir, and all recovered without apparent sequala.

There was a single case reported from Missouri[8] on September 6, 2024, with no immediately apparent occupational or animal exposures. The patient had been hospitalized due to what was thought to be his underlying medical conditions. The patient was treated with influenza antivirals, discharged, and fully recovered. This case was identified through

[5] Finland to start bird flu vaccinations for humans, in world first | Reuters Accessed September 26, 2024
[6] CDC Reports Fourth Human Case of H5 Bird Flu Tied to Dairy Cow Outbreak | CDC Online Newsroom | CDC Accessed September 25, 2024
[7] CDC Confirms Human Cases of H5 Bird Flu Among Colorado Poultry Workers | CDC Online Newsroom | CDC Accessed September 26, 2024
[8] CDC Confirms Human H5 Bird Flu Case in Missouri | CDC Newsroom Accessed September 26, 2024

the state's seasonal influenza surveillance system and reported to CDC. No ongoing transmission among close contacts or medical workers were identified although one contact and two health care workers were reported to be symptomatically ill, but testing for avian influenza virus was negative and serology is pending.[9]

Outside the U.S., the number of documented human cases of H5N1 clade 2.3.4.4b influenza infection or disease have been rare. In 2022, two asymptomatic poultry workers had low levels of viral RNA detected in nasopharyngeal swab specimens that were attributed to environmental contamination in Spain. In England, between 2021 and 2023, nasopharyngeal swabs collected from asymptomatic persons with poultry exposures with 5 having low levels of viral RNA detected. More recently, in 2023 there have been five cases of zoonotic infections: one in Ecuador (2.3.4.4b clade), one in China (2.3.4.4b clade), two in Cambodia (2.3.2.1c clade), and one in Chile (2.3.4.4b clade). A few of these cases have been severe and some were fatal.

A cautionary note comes from the case of a recent Cambodian 15-year-old female who died from H5N1 avian influenza. This case involved the surface typing of the older H5 2.3.2.1c clade seen throughout Southeast Asia, but notably the virus that infected the individual is a novel reassortant that includes internal genes from the newer H5 2.3.4.4b clade.[10] It is not known whether this represents a new evolutionary change of the virus.

2.3 U.S.-licensed and EMA-marketing authorized influenza vaccines

Four manufacturers (AstraZeneca, GlaxoSmithKline, Sanofi Pasteur, and Seqirus) of seasonal influenza vaccines have licensed influenza vaccines in the U.S. These four manufacturers produce ten different formulations of trivalent seasonal influenza vaccines, including an intranasal formulation. These manufacturers also have eight different quadrivalent formulations licensed with FDA.

Currently three pandemic Influenza A H5N1 monovalent virus vaccines, containing prototype influenza strains that are either from clade 1 or clade 2.2.1, are licensed in the U.S. (for basis of licensure, see Section 3 and Section 4 below). Several candidate Influenza (H5N8) A/Astrakhan/3212/2020 (clade 2.3.4.4b) vaccines are currently undergoing evaluation.

The European Medicine Agency (EMA) has authorized six pandemic Influenza A H5N1 vaccines that contain prototype influenza strains from either clade 1 or clade 2.2.1, as well as authorized one pandemic Influenza A H5N8 clade 2.3.4.4b monovalent vaccine.

A summary of currently available U.S.-licensed and EMA-marketing authorized vaccines:

Manufacturer	**Proprietary Name**	**Strain Description**	**Adjuvant**	**Manufacturing Substrate**	**Regulatory Authority** (Approval year)
Sanofi Pasteur	-	A/Vietnam/1203/2004 (H5N1, clade 1)	-	Egg	FDA (2007)

[9] CDC A(H5N1) Bird Flu Response Update September 27, 2024 Accessed October 1, 2024
[10] Cambodia's recent H5N1 case involved novel reassortant | CIDRAP (umn.edu) Accessed September 26, 2024

GSK	Q-Pan	A/Indonesia/05/2005	AS03	Egg	FDA (2013)
Seqirus	Audenz	A/turkey/Turkey/1/2005 (NIBRG-23)	MF59C.1	MDCK cells	FDA (2020)
Seqirus	Celldemic	A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) (clade 2.2.1)	MF59C.1	MDCK cells	EMA (2024)
Seqirus	Incellipan	A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23)	MF59C.1	MDCK cells	EMA (CMA* 2024)
Seqirus	Zoonotic	A/Astrakhan/3212/2020 (H5N8)-like strain (CBER-RG8A) (clade 2.3.4.4b)	MF59C.1	Egg	EMA (2023)
Seqirus	Aflunov	A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) (clade 2.2.1)	MF59C.1	Egg	EMA (2010)
Seqirus	Foclivia	A/Vietnam/1194/2004 (H5N1)	MF59C.1	Egg	EMA (2009)
GSK	Adjupanrix	A/Vietnam/1194/2004 (H5N1)-like strain (NIBRG-14)	AS03	Egg	EMA (2009)
AstraZeneca	-	A/Vietnam/1203/2004 (H5N1)	-	Egg	EMA (2016)

*CMA: conditional market authorization

3. Prototype Influenza A H5N1 Vaccine Approval Process to Date

In February 2007, VRBPAC discussed a monovalent H5N1 vaccine (Influenza Virus Vaccine, H5N1) manufactured by Sanofi Pasteur Inc. 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. In April 2007, CBER approved 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. Implicit in the approval was that effectiveness data for Fluzone supported that of the H5N1 vaccine. This vaccine is included in the Strategic National Stockpile.

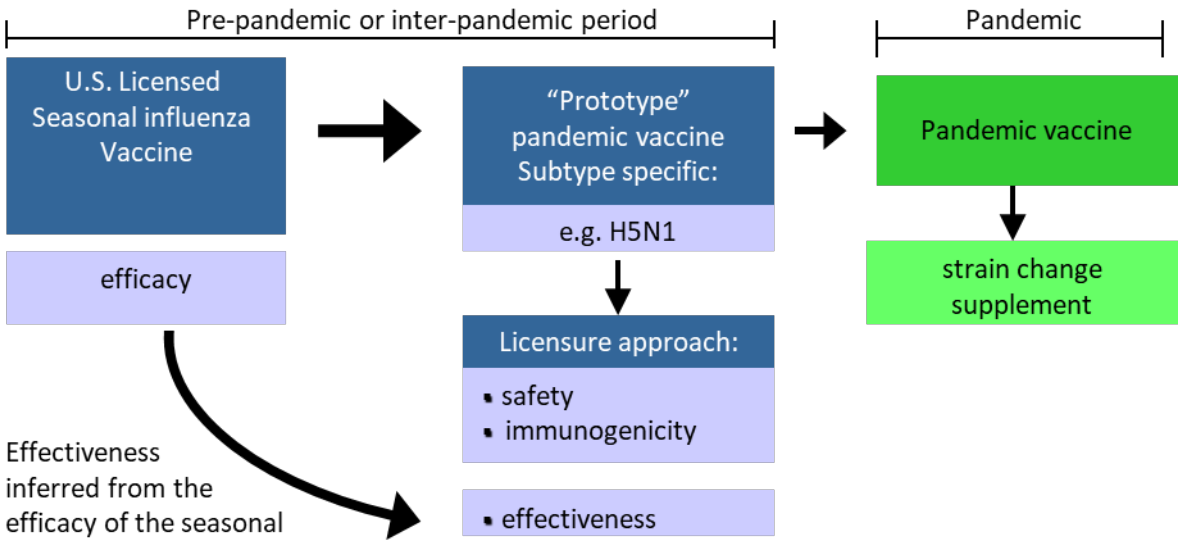
Similar traditional approval pathways were used for U.S. licensure of the other two prototype H5N1 pandemic vaccines. In 2013, Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted manufactured by ID Biomedical Corporation of Quebec and distributed by GlaxoSmithKline (GSK) was approved for use in persons (6 months and older) at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. In 2020, Influenza A (H5N1) Monovalent Vaccine, Adjuvanted manufactured by Seqirus, Inc. was approved for use in persons 6 months of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

4. Strain Change of U.S-licensed Prototype Pandemic Vaccines During a Declared Pandemic

As proposed by Weir and Gruber (2016)[11] and depicted in the schematic diagram below, effectiveness of a prototype pandemic influenza vaccine is inferred from demonstrated

[11] Weir and Gruber (2016) An overview of the regulation of influenza vaccines in the United States. *Influenza and Other Respiratory Viruses* 10(5), 354–360.

efficacy of a licensed seasonal vaccine made by the same manufacturing process and supported by clinical studies of safety and immunogenicity of the prototype pandemic vaccine. During a pandemic, the prototype pandemic vaccine license can be updated with a strain change of the same HA subtype in a process similar to that used for updating seasonal vaccines.



In the event of a pandemic, and following WHO and VRBPAC recommendations, manufacturers of U.S-licensed prototype pandemic vaccines would submit a "strain change supplement" for regulatory review of their updated pandemic vaccine, including complete chemistry, manufacturing, and control information for the updated vaccine to ensure product quality and consistency; and nonclinical data to support effectiveness of the updated vaccine. FDA may require clinical immunogenicity and safety data be provided post-approval. Sponsors should expect FDA to seek their involvement in working with FDA and other governmental agencies on plans to collect additional safety and effectiveness data, such as through epidemiological studies, when the vaccine is used. The additional data may allow a better understanding of the relationship between immunogenicity of the vaccine and clinical effectiveness. (See Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines | FDA)

5. Proposed Process for Updating Pandemic Influenza Vaccines in the Inter-Pandemic Period

While a well-defined regulatory pathway, such as that described in Section 4 above, exists to make available better matched pandemic influenza vaccines for use during a pandemic, the appropriate timing and processes to make available, based on previously licensed prototype pandemic influenza vaccines, better matched pandemic influenza vaccines prior to a pandemic are currently under discussion as part of HPAI virus pandemic preparedness. This discussion is particularly timely in the context of the current inter-pandemic period for prototype influenza A (H5) monovalent vaccines-- that is, subsequent to the original licensure of prototype influenza A (H5) monovalent vaccines but prior to a potential influenza A H5N1 pandemic or declared public health emergency.

Such an inter-pandemic period process for updating pandemic influenza vaccines could include the following:

- A VRBPAC discussion as to whether a change to the current composition of a licensed prototype vaccine is needed for preparedness purposes and whether candidate vaccine viruses are available that are appropriate for an update to licensed prototype vaccines
- Preparation and submission of a data package for an updated pandemic vaccine by manufacturers of licensed pandemic vaccines for regulatory review, to include:
    - Chemistry, manufacturing, and control data for the updated vaccine to ensure product quality and consistency;
    - Clinical immunogenicity and safety data for the updated vaccine.

Should a pandemic situation develop and a public health emergency declared, VRBPAC would be reconvened to make a final composition recommendation.

As part of HPAI virus pandemic preparedness, including considerations for updating the composition of prototype influenza A (H5) monovalent vaccines, FDA is requesting that VRBPAC discuss and provide input on a proposed strain change process and expected data requirements for updating licensed prototype pandemic influenza vaccines during the inter-pandemic period.

6. Summary

A critical component of pandemic preparedness and planning is licensure of prototype pandemic influenza vaccines. Prior to a pandemic and in the absence of transmission of non-seasonal influenza A virus subtypes (e.g., H5) sufficient to demonstrate vaccine effectiveness in pre-licensure clinical studies, licensure of a prototype pandemic influenza vaccine may be inferred from demonstrated efficacy of a licensed seasonal vaccine made by the same manufacturing process and supported by clinical studies of safety and immunogenicity of the prototype pandemic vaccine. Currently three prototype pandemic Influenza A H5N1 monovalent virus vaccines, containing either H5N1 clade 1 or clade 2.2.1 virus, are licensed in the U.S. via this regulatory pathway. In the event of a pandemic or declared public health emergency, prior licensure of prototype pandemic vaccines may permit approval of pandemic influenza vaccines of the same hemagglutinin A subtype as "strain change supplements" in a process similar to that used for updating seasonal influenza vaccines. Manufacturers of updated pandemic influenza vaccines would be expected to work with FDA and other governmental agencies on plans to collect additional safety and effectiveness data during pandemic vaccine deployment.

FDA is requesting that VRBPAC consider a proposed strain change process and the expected data requirements for updating the composition of licensed prototype pandemic influenza vaccines during the inter-pandemic period—that is, subsequent to original licensure of prototype pandemic influenza vaccines but prior to a pandemic or declared public health emergency. Specifically, FDA requests VRBPAC to discuss and provide input on a proposed strain change process for prototype influenza A (H5) monovalent vaccines in the context of the current inter-pandemic period. When considering an inter-pandemic composition update to U.S.-licensed prototype influenza A (H5) monovalent vaccines, VRBPAC discussion topics include: if/when a change is needed to the composition of

licensed prototype H5 vaccines; what available evidence is needed to support the selection of currently available candidate vaccine strains for a possible update to U.S.-licensed prototype H5 vaccines; and, reconvening VRBPAC to make a final composition recommendation if/when an influenza A H5N1 pandemic is declared.

7. Discussion Topics

- Please discuss and provide input on the proposed strain change process during the inter-pandemic period.
- Please discuss whether a change to the current composition of a licensed prototype vaccine using this process is needed for preparedness purposes and whether candidate vaccine viruses are available that are appropriate for an update to licensed prototype vaccines