February 21, 2008: Day 2, Session II

CONTINUING DISCUSSIONS ON PANDEMIC/PRE-PANDEMIC VACCINE DEVELOPMENT

I. INTRODUCTION

In February of 2007, the Center for Biologics Evaluation and Research (CBER) convened the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss, among other influenza issues, the topic of influenza vaccine development for pandemic and pre-pandemic indications. Moreover, at that time, the primary focus of our discussion was on the types of clinical studies that may be needed to support such indications. Subsequently, more data are now available for influenza vaccines against different subtypes of H5N1, and many of these vaccines are being formulated with novel adjuvants; thus, additional issues and concerns have arisen for the development, evaluation and use of these vaccines against influenza strains with pandemic potential. CBER's thinking continues to evolve on approaches to evaluate influenza vaccines for pandemic and pre-pandemic use, and we would like to provide you with an update on our current position. We will focus on two important issues relating to the assessment of vaccines against influenza strains having pandemic potential for use during a pandemic, and/or for use in the pre-pandemic period. The two topics we will present for discussion are: 1) defining pandemic and pre-pandemic influenza vaccine indications and what types of data would support the latter, and 2) outlining the regulatory pathway for developing and evaluating adjuvanted influenza vaccines against viruses with pandemic potential.

II. BACKGROUND

Reference is made to the February 27, 2007, VRBPAC meeting. Please see Appendix 1 for a brief summary of the presentations made at the February 27, 2007, VRBPAC session entitled "Clinical Development of Influenza Vaccine for Pre-Pandemic Use" as background for this briefing document. The complete transcripts of the February 27-28, 2007, VRBPAC can be found at the following website:

http://www.fda.gov/ohrms/dockets/ac/cber07.htm#VaccinesandRelatedBiological

Since last February 2007, CBER finalized two Guidance to Industry documents, entitled "*Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines*," and "*Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*."[1, 2] CBER also licensed Sanofi Pasteur's H5N1 Influenza Virus Vaccine as the first US licensed influenza vaccine for a pandemic indication.[3] This vaccine is maintained in the Strategic National Stockpile. Postmarketing commitments for additional data are being obtained. CBER opened a public docket on October 3, 2007, to receive information and comments from manufacturers of vaccines and interested persons concerning the development of

safety and effectiveness assessments of vaccines used for pandemic influenza.[4] Responses from external stakeholders currently are being collected and assessed. CBER also organized a Public Workshop for Immune Correlates of Protection Against Influenza A Viruses in Support of Pandemic Vaccine Development, which was held December 10-11, 2007. This workshop was co-sponsored by FDA/CBER, NIH/NIAID, and the World Health Organization to review data, identify gaps, and recommend a global research agenda to improve vaccine efficacy assessment, including the identification of surrogate markers likely to be predictive of clinical benefit as well as development of appropriate surrogate assays. A summary of that meeting is included in this package (Appendix II). Finally, CBER has been working with many manufacturers on their development plans for vaccines against influenza strains of pandemic potential. These interactions have given rise to the two areas of discussion mentioned earlier.

III. DEFINING AND SUPPORTING PANDEMIC AND PRE-PANDEMIC INDICATIONS FOR INFLUENZA VACCINES

The terms "pandemic influenza vaccine" and "pre-pandemic influenza vaccine" have been used in a variety of ways among industry, scientists, and regulators. We will attempt to clarify our use of these terms based upon defining the indication sought, and will explain the type of information needed to support each indication. The proposed indication or intended use of the influenza vaccine under development will determine the type of clinical data needed to support the safe and effective use of the vaccine. Accordingly, when discussing the development of vaccines targeted against influenza strains of pandemic potential, it is important to consider whether the vaccine is being developed for use during the pandemic, i.e., a pandemic indication, or for use in the interpandemic period, i.e., a pre-pandemic indication.

The nomenclature of "pandemic" and "pre-pandemic" is complicated by the time period in which these vaccines are developed. We are currently in the interpandemic period, which includes the pandemic alert period, more commonly referred to as the "pre-pandemic" period. Vaccines with both pandemic and pre-pandemic indications are now being developed during this interpandemic period.

The definitions of "pandemic" and "pre-pandemic" proposed by CBER are specific to the indication sought and set forth below. Of note, the WHO and EMEA do not define these terms as they relate to an indication or usage.[5,6]

Pandemic Indication: Vaccines licensed for a pandemic indication are intended to be used to immunize persons who are at high risk of exposure to an influenza virus strain of pandemic potential. Examples of high risk exposure include the emergency immunization of persons during a pandemic, or the immunization of personnel deployed to areas where cases of human-to-human or animal-to-human transmission of a novel influenza virus of pandemic potential is occurring. In the U.S. a vaccine with a pandemic indication most likely will be stockpiled by public health authorities for use in a public health emergency as declared by the U.S. Secretary of

Health and Human Services under Section 319 of the Public Health Service Act. As risk/benefit considerations differ in high-risk and non-high risk scenarios, the data needed to support safety and efficacy in these scenarios also will vary. The *FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines* describes what data are recommended for sponsors to submit in a biologics licensing application. (Appendix III).

Circumstances of the situation in which a vaccine with a pandemic influenza indication will be used help define ideal characteristics for such a vaccine. Such characteristics may include preference for a single dose during emergency deployment, rapid induction of an adequate immune response, and immunity that sustains through waves of the pandemic.

Pre-pandemic Indication: Vaccines with a pre-pandemic indication are intended for the active immunization of persons against influenza virus subtypes of pandemic potential during the period when these subtypes have not yet evolved the capacity for sustained and efficient human-to-human transmission (the interpandemic time period). Influenza vaccine used in this way represents a strategy for population-based pandemic influenza preparedness.

Influenza vaccines with a pre-pandemic indication will ideally stimulate sustained immunological memory to enable boosting, resulting in an adequate immune response at a much later time point. Sustained immunological memory that can be boosted a year or more later is desirable for a preparedness strategy. The risks must be relatively low for a vaccine with a pre-pandemic indication because in the absence of a pandemic, the benefit of the vaccine will be difficult to assess. There are currently no U.S. licensed influenza vaccines with a pre-pandemic indication, but manufacturers also have expressed interest in developing vaccines for this use.

Clinical Development

General Clinical Trial Design

In general, immunogenicity trials for pandemic and pre-pandemic indications for influenza vaccines are prospective, randomized, double-blinded and controlled.

Study Population

For pandemic and pre-pandemic indications, initial studies may start in adults (e.g., persons 16 to 64 years of age). Subsequent pediatric and geriatric studies to determine dosing most likely will be needed for both pandemic and pre-pandemic indications. For sponsors developing vaccines for a both pandemic and pre-pandemic indication using novel adjuvants, it will be particularly important to have adequate safety information prior to initiating studies in children.

Immunogenicity Assessment

Pandemic vaccine immunogenicity endpoints and the criteria to measure the endpoint response are outlined in the current *FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines*. This Guidance recommends use of seroconversion rates (defined as the percentage of subjects with a pre-vaccination hemagglutination inhibition (HAI) titer of <1:10 and post-vaccination titer of ≥1:40 or a pre-vaccination titer ≥ 1:10 with a 4-fold or greater rise in HAI titer post-vaccination) and the percentage of subjects with post-vaccination titers ≥1:40 as the co-primary endpoints for the study of vaccines for a vaccine with a pandemic indication. The criteria for successful attainment of these endpoints are:

1. For seroconversion rate: lower bound of the two-sided 95% confidence interval ≥ 40% in adults younger than 65 years of age, and ≥ 30% in persons 65 years of age and older, and
2. For percentage of subjects with post-vaccination HAI titer ≥1:40: lower bound of the two-sided 95% confidence interval ≥ 70% for adults less than 65 years of age, and 60% for adults 65 years of age and older.

While the Guidance does not specify the time after vaccination at which immunogenicity should be assessed, these determinations generally have been made at 21-28 days following vaccination (as was the case for the sanofi pasteur H5N1 influenza vaccine approved for a pandemic indication). Durability of immune responses that will persist through the expected waves of the pandemic is desirable.

Although the Guidance does not outline the specific requirements for evaluating an influenza vaccine for a pre-pandemic indication, the immune response elicited by the first dose should be able to be boosted by subsequent doses of vaccine at much later time-points. Vaccine recipients should be followed long enough to measure a boost in the immune response. At the February 2007 VRBPAC meeting, recommendations included measurement of immunogenicity endpoints at 21-28 days, 6 months, and one year post-vaccination and longer. Therefore, intended use of an influenza vaccine with a pre-pandemic indication for the purpose of population preparedness may depend on its ability to be boosted after initial dose(s) that prime the immune system. To be a useful preparedness strategy, it may be necessary to demonstrate after a year or more from the initial priming dose(s) that a person has been adequately boosted as measured by an appropriate immune response. An appropriate immune response after the priming dose(s) may be different from that which is deemed acceptable for a later response to a vaccine boost. For example, a lower degree of responsiveness may be considered adequate if a later response to a vaccine boost proves to be robust.

For VRBPAC Consideration:

CBER would like feedback from the VRBPAC regarding the appropriate immune response after an initial priming dose(s) with an influenza vaccine for pre-pandemic

use in relationship to the boost response from subsequent doses of the same vaccine. Would the same criteria used for assessing the immune response for pandemic use be appropriate for assessing antibody response for pre-pandemic priming? For pre-pandemic boosting?

IV. DEVELOPMENT PATHWAY FOR INFLUENZA VACCINES WITH A PANDEMIC INDICATION THAT CONTAIN NOVEL ADJUVANTS, INCLUDING THE ACCELERATED APPROVAL PATHWAY

Future vaccines for influenza strains with pandemic potential will likely be adjuvanted, given the antigen-sparing properties, enhanced immunogenicity, cross-protection, and other properties observed from studies with adjuvanted vaccines.[7] CBER has stated in the pandemic influenza Guidance that we may consider these vaccines for licensure under the accelerated approval mechanism, with HAI titers serving as a "reasonably likely" predictor of clinical benefit (21 CFR 601 Subpart E). Accelerated approval may be granted for certain biological products such as influenza vaccines for pandemic use when such vaccines have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and provide meaningful therapeutic benefit over existing treatments. Such an approval will be based on adequate and well-controlled clinical trials establishing that the vaccine has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Under accelerated approval, applicants are required to verify and describe the clinical benefit of the vaccine. Adequate and well-controlled post marketing efficacy studies must be performed with due diligence in order to confirm clinical benefit of the vaccine, If the postmarketing clinical study fails to verify clinical benefit, marketing approval for vaccine may be withdrawn by the Agency.

Sponsors seeking approval of an adjuvanted seasonal influenza vaccine through traditional approval may be able to use these data in support of confirming the clinical benefit of an influenza vaccine for pandemic use if the vaccines are manufactured by the same process. Other approaches to demonstrating clinical benefit may be possible and sponsors desiring to pursue alternative approaches should discuss their plans with CBER early in the developmental stages.

Establishing Initial Dose of the Adjuvant

Regarding adjuvanted vaccines and the selection of the initial dose, the pandemic influenza Guidance states on page 13:

"For initial dose and formulation selection, a comparative clinical study of adjuvanted vs. non-adjuvanted vaccines that both contain the same amount of antigen should demonstrate that the immune response elicited by the adjuvanted antigen is better than that elicited by the same antigen alone. For differences in HAI antibody titer and seroconversion rates, the lower confidence limit on the appropriate point estimate excluding equality (i.e., the value 1 for the ratio

parameter or 0 for the difference parameter) may be sufficient to demonstrate the added value of the adjuvant.

A comparative study of an adjuvanted vaccine containing a lower amount of antigen than the dose-optimized non-adjuvanted vaccine formulation may be conducted to demonstrate non-inferior immune responses elicited by the adjuvanted vaccine. Other approaches to demonstrate the value of the adjuvant, such as a greater ability of an adjuvanted vaccine to induce antibodies that cross-react with a wider variety of subtypes, strains, or clades, when compared to an unadjuvanted vaccine, may be possible. Sponsors are encouraged to discuss their proposals with CBER.

Selection of an appropriate dose and formulation should also be guided by the safety profile of the formulations and regimens being studied."

Influenza vaccines with a pandemic indication that only need one dose, may provide long-term immunogenicity alleviating the need for boosters, and that cross-protect against varying antigenic changes are desirable from a public health stand point. Formulating these vaccines with adjuvants may be able to provide some of the benefits mentioned. Studies of adjuvanted vaccines will likely benefit from exploration of dose optimization for a single administration, duration of immunity, ability to cross-neutralize various antigens, as well as other characteristics. During this inter-pandemic period, we should take this opportunity to gather information to help characterize these factors. In addition, safety considerations may arise from the exposure to multiple adjuvants (or multiple exposures to these novel adjuvants), due to various adjuvanted vaccines each containing its own unique adjuvant, and the potential of repeated exposure to these adjuvants.

As clinical development proceeds to Phase 3 studies, and in the absence of clinical endpoint studies being conducted during a pandemic to confirm the contribution of an adjuvant to protection from disease, it may be necessary to demonstrate superior immunogenicity of an adjuvanted vaccine over its non-adjuvanted counterpart using more rigorous criteria. The criteria for demonstrating equivalence may be, for example, that the GMTs for HAI responses of two vaccines at the end of the vaccination series be within 2-fold of one another. Consequently, criteria for superiority might be set to exclude equivalence (i.e., lower bound of the two-sided 95% Confidence Interval of the ratio $GMT_{adjuvant}/GMT_{no\ adjuvant}$ must be >2). Additionally, for some vaccines, CBER has used a difference in seroresponse rates of less than 10% as evidence of equivalent or non-inferior immune responses. Therefore, to demonstrate a superior response rate following vaccination with an adjuvanted product, criteria might be set such that the response rate of a vaccine with adjuvant is at least 10% higher than the vaccine formulated without adjuvant, and thus exclude a conclusion of similar response rates (i.e., lower bound of 95% CI on the proportion with HAI >1:40 in the adjuvanted vaccine group minus the proportion >1:40 in the non-adjuvanted vaccine group must be >10%).

Safety Assessment

The size of the safety database needed for licensure will depend on:

- the indication being sought,
- the inclusion of an adjuvant,
- the identification of safety signals in pre-clinical or clinical studies, and
- the available safety data from a seasonal influenza vaccine manufactured with the same process (and adjuvants) as the influenza vaccine against strains of pandemic potential under consideration.

Many manufacturers are developing influenza vaccines for pandemic or pre-pandemic indications with novel adjuvants to improve immunogenicity, particularly for vaccines against H5N1. Worldwide marketing experience for these novel adjuvants may be very limited or absent. Therefore, it may be necessary to conduct large simple safety studies with avian influenza vaccines that are formulated with novel adjuvants. Additionally, it could be advantageous to obtain safety information using a seasonal analogue, particularly if the influenza vaccine is formulated with a novel adjuvant, and developed for a pre-pandemic indication. The pre-marketing safety database alone will need to ensure that risks are low relative to theoretical benefits specific for either indication.

At the current time, CBER expects a minimum six months post-vaccination safety follow-up for egg-derived inactivated vaccines with a pandemic indication. If pre-clinical and clinical data raise safety concerns, a safety follow-up period of one year or more may be needed, particularly for vaccines with a pre-pandemic indication and vaccines with novel adjuvants.

Postmarketing safety surveillance data of other influenza or non-influenza vaccines utilizing similar adjuvants or manufacturing processes will also be important to consider in the evaluation of the BLA. In the current interpandemic period, there is time to obtain an adequate safety database for both pandemic and pre-pandemic indications, especially for formulations containing novel adjuvants and manufacturing processes. For the pre-pandemic indication it will be especially important to define vaccine risks and ensure low incidence of serious adverse events. The assessment of safety post-licensure will be included as a post-marketing commitment for all licensed novel influenza vaccines with pandemic or pre-pandemic indications.

For VRBPAC Consideration:

Please comment on whether it is reasonable to use an analogous adjuvanted seasonal vaccine to infer efficacy for an adjuvanted influenza for pandemic use. In the absence of an available analogous adjuvanted seasonal product, please discuss other possible studies that could be done to confirm efficacy. Please discuss the option of

licensing adjuvanted influenza vaccines for pandemic use solely on the basis of immunogenicity.

Please comment on CBER's proposal to evaluate the clinical effect of adjuvanted influenza vaccines over non-adjuvanted vaccines. What alternative or additional criteria would you recommend for demonstrating superiority of an adjuvanted vaccine in the absence of clinical efficacy endpoints?

V. CONCLUSION

We acknowledge that there are many additional issues related to the development of influenza vaccines for pandemic and pre-pandemic use; however, given the time constraints, we have limited our focus to two issues for this particular session of VRBPAC. CBER looks forward to VRBPAC and open public discussion on the two main areas of discussion:

- Indications: Pandemic versus Pre-pandemic
- Development Pathway of Adjuvanted Influenza Vaccines against Viruses of Pandemic Potential

We will continue to update the VRBPAC on pandemic- related influenza issues and seek your input and advice at future meetings.

APPENDIX I

Summary of Feb. 27, 2007 VRBPAC: Clinical Development of Influenza Vaccines for Prepandemic Uses

The synopses below are being provided as background to this briefing document.

A. Dr. Nancy Cox of the Centers for Disease Control and Prevention presented information relevant to the continuing and sustained cases of avian influenza outbreaks throughout SE Asia. Between December 2003 and February 2007, nine SE Asian countries reported a total of 275 human cases with 167 deaths, which is an overall case fatality of approximately 60%. The common denominator, thus most likely risk factor, in all cases was direct human exposure to sick or dead birds. In response to this critical public health concern, the World Health Organization (WHO) assumed a leadership role through the four WHO Collaborating Centers and the four additional H5 Reference Laboratories to generate suitable H5 reference viruses, as well as necessary reagents, for pandemic vaccine development.

B. Dr. Jesse Goodman, Director, CBER, presented the considerations for pre-pandemic and early pandemic use of influenza vaccines, including strategies to speed vaccine production and availability. It was noted during Dr. Goodman's talk that a vaccine which is an exact match to a circulating pandemic strain, may not be available until 6 months after identification of this strain. As such, it is important to consider in our preparedness planning, strategies for effective stockpiling and deployment, as well as considerations on how to "maximize" cross-protection from stockpiled vaccines. With that said, however, caution should be exercised, as the benefit/risk ratio is much clearer for pandemic use of vaccine, as opposed to pre-pandemic use. Preliminary discussions for data needs on pre-pandemic use are warranted at this time to provide transparency to the public and clarity to the external stakeholders developing vaccines using influenza viruses of pandemic potential.

C. Dr. Joseph Toerner, Team Leader, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, CBER, presented a brief overview of the FDA draft guidance on clinical data needed to support licensure of pandemic influenza vaccines and expounded on the need for further discussion and guidance regarding pre-pandemic use of influenza vaccines. The issues mainly centered upon clinical trial design for prime-boost, endpoints (including cross-protective and clinical benefit), durability of immune response, and the size of a safety database needed to support pre-pandemic use. There was also some discussion on the serological assays used to evaluate human immune response.

D. Dr John Treanor, Professor of Medicine, University of Rochester, presented preliminary data regarding the immune responses of subjects previously vaccinated eight years ago with a baculovirus-derived, purified, recombinant hemagglutinin

(rHA) vaccine based on A/Hong Kong/156/97 and revaccinated 8 years later with the sanofi-pasteur H5N1 inactivated vaccine based on the reverse-genetics derived A/Vietnam/1203/04.* Whereas previous data reported that subjects who received a third dose six months after the first and second vaccinations with the same vaccine had antibody levels that were only boosted back to levels as high as post-second vaccination, Dr. Treanor demonstrated in N=37 subjects, that a single dose of A/Vietnam vaccine boosted the A/Hong Kong rHA primed individuals higher that those "unprimed" individuals who were in the three-dose regimen homologous vaccine study, thereby suggesting that heterologous prime–boost may be a promising preparedness strategy.

* Goji NA, Nolan C, Hill H, Wolff M, Rowe T, Treanor JJ. *Immune Responses of Healthy Subjects to a Single Dose of Intramuscular Inactivated Influenza A/Vietnam/1203/2004 (H5N1) Vaccine After Priming with an Antigenic Variant.* 44th Annual IDSA Meeting, 2006.

APPENDIX II

FDA/NIH/WHO Public Workshop (December 10-11 2007, Bethesda, MD):

Immune Correlates of Protection Against Influenza A Viruses in Support of Pandemic Vaccine Development

Organizers: Jerry Weir (CBER), Hana Golding (CBER), Maryna Eichelberger (CBER), Maureen Hess (CBER), Kanta Subbarao (NIAID), Catherine Luke (NIAID), David Wood (WHO), Martin Friede (WHO)

The goals of the public workshop were to (1) identify the gaps in our knowledge and abilities in addressing the unique challenges encountered in the development and evaluation of vaccines intended to protect against pandemic influenza, and (2) facilitate implementation of global research agenda to improve efficacy assessment of pandemic influenza vaccines.

This public workshop included discussions on:

- Current knowledge regarding correlates of protection against seasonal influenza
- Immune responses to avian influenza infection and vaccines for novel influenza viruses in humans
- Assays to evaluate vaccine immunogenicity
- Evaluation of avian influenza vaccine efficacy

This summary presents a synopsis of the sessions with key points that were made by the speakers.

The points expressed in the workshop were those of the presenters and not necessarily the views of the U.S. Food and Drug Administration of the U.S. governemet

Session I. Correlates of protection against seasonal influenza
(Chair: Robert Couch, speakers: Robert Couch, Brian Murphy, Tom Jefferson, Jack Bennick, and Harry Greenberg)
This session included presentations on humoral and cellular immune responses against seasonal influenza infections and vaccines, including inactivated vaccines (TIV) and live attenuated cold adapted vaccines (LAIV).

Characteristics of Immunity:

- Homotypic immunity is powerful and long lived
- Immunity varies with the extent of antigenic variation (antigenic drift)
- Protection correlates with serum antibodies against the hemagglutinin (HA) of the infecting virus
- Anti-HA antibodies may block viral infection, reduce viral replication in the upper respiratory tract and prevent dissemination to the lung.

Secretory IgA is likely the most relevant antibody in the upper respiratory tract, but serum IgG is protective in the lungs.

- The measurement of antibodies in mucosal secretions is difficult (identified as a key research priority). Therefore, studies on correlates of immunity have almost exclusively focused on serum antibodies
- Anti-NA antibodies reduce the severity of infection if present in secretions
- Anti-M2 antibodies reduce the severity of infection in mice; titers in humans are low and proof of the value of anti-M2 in resolving infections is lacking
- Passive transfer of immune sera in mice provides greater protection against infection in the lower respiratory tract than upper respiratory tract, presumably reflecting the site of transudated IgG
- Heterosubtypic immunity (HSI, protection against influenza strains that have a different HA subtype) is weak in humans
- T cell responses against internal (more conserved) viral proteins contribute to HSI in mice. These responses do not prevent infection but reduce virus titers and protect against lethality or reduce signs of disease.
- T cell responses are often targeted to limited immunodominant epitopes based on antigen processing, HLA binding, and TCR binding affinities. There is limited information about the specificity and characteristics of influenza-specific T cell responses in humans.
- Studies of human cellular immunity after vaccination with LAIV and TIV showed
- an increase in the mean percentage of influenza-specific IFN-γ-producing CD8 T cells in children following immunization with LAIV. A similar increase was not evident in adults, although there was a reproducible increase if activation phenotype (CD38) was also considered. No increase in CD8+ T cell responders was observed in either children or adults following immunization with TIV.
- Influenza-specific effector IgA and IgG antibody secreting cells (ASC) that are measured in the circulation following vaccination show that this is useful method to examine vaccine immunogenicity. TIV, but not LAIV, significantly increased the percent of circulating memory B cells measured 30 days after vaccination. antibody responses and the number of antibody secreting cells (ASC) were more significant in children.
- Influenza-specific CD4+ T cell responses were predictive of antibody responses.
- There is no single end-point that can be used as a surrogate of protection; protection reflects the sum of various immune responses, including antibody and cell-mediated responses
- For evaluation of clinical trials of influenza vaccines, a serum HI antibody titer of 40 is accepted as the level of serum HI antibody associated with >50% reduction of the risk of contracting an influenza infection or influenza disease. However, it should be kept in mind that

other immune parameters also contribute to protection so that HAI titer does not necessarily guarantee immunity or predict susceptibility.
- Clinical trials to determine vaccine efficacy should be designed carefully to avoid risk of bias and should be reported accurately.

Session II. Immune responses to avian influenza infections and vaccines for novel influenza viruses in humans
(chair: Jacqueline Katz, speakers: Nancy Cox, Jacqueline Katz, Maria Zambon, David Cho, Ruth Karron, Laszlo Palkonyay, and Frederick Hayden)
This session included talks on the status of avian influenza infections in humans, a description of immune responses in poultry workers and description of clinical trials that have evaluated inactivated and live attenuated avian influenza vaccine candidates.

Avian H5N1 influenza viruses in birds and human exposure:

- H5N1 viruses in birds: there is extensive genetic and antigenic heterogeneity, with 9 of 10 different genetic clades isolated in the past 3 years. A unifying classification of H5N1 viruses has been established by WHO/FAO/OIE
- H5N1 infections in humans: as of November 14, 2007, 335 human infections were reported of which 206 were fatal (61.5%). The human infecting viruses reflect the heterogeneity in birds
- Sensitivity to amantadine varies among the clades: clade 1 (Vietnam like) and clade 2.1 (Indonesia-like) are 96% and 86% resistant, while clades 2.1 and 2.2 viruses are only 6% and 10% resistant.
- Receptor binding specificity: the fine specificity of H5 can be assessed by glycan array technology. Most human H5N1 virus isolates bind to sialic acid (SA) linked via □2-3 >> □2-6, while seasonal influenza strains bind to SA □2-6 >> □2-3. This difference correlates with the restricted human to human transmission of H5N1 observed to date. However, glycan array studies revealed more complex binding patterns for various avian influenza isolates.
- Reverse genetics has been used to generate 6:2 PR8 reassortants representing each clade (1,2,3) and subclade (2.1; 2.2; 2.3). These can be used for potential vaccine development and *in vitro* assays to evaluate antibody cross reactivity; removal of the multibasic cleavage site of the HA is necessary to permit handling of the vaccine virus seeds at BSL-2.
- Serological responses to avian influenza viruses in poultry workers were low: after the 1997 H5N1 outbreak, neutralizing titers ranged between 1:10-1:40, while titers of $\geq$ 1:80 were associated with more intense exposures.
- Seroprevalence of anti-H5 antibodies is low in populations exposed to infected birds; antibody titers in mild/asymptomatic infections are short-lived
- Following exposure to H7N3 in Canada, serum neutralizing antibodies were not detected in the 2 individuals with confirmed H7 infection;

microneutralization assay was not used to measure titers in sera of individuals exposed to H7N7 in the Netherlands – a modified HAI test demonstrated seroconversion in approximately half of these individuals

- Exposure to H9N2 strains prompted examination of responses to the G1 and G9 lineages of H9 in poultry workers in Hong Kong. While only 2% were positive for G1, approximately 36% were positive to G9. Reactivity with G9 reflected the presence of age-related pre-existing antibodies to H2 that are cross-reactive with H9.

WHO Clinical Research Initiative:
Human surveillance in areas with high incidence of wild birds->poultry/domestic birds transmissions:

- WHO has established the South East Asia Influenza Clinical Research Network through considerable international collaborative efforts. The aim of this group is to support clinical protocol-based studies to improve the understanding of pathogenesis, immunology, diagnostics, and therapeutics (NA-inhibitors) for human H5N1 infections. An influenza co-coordinator will develop central inventory of resources that can be shared between groups. This may facilitate studies to determine neutralizing antibody titers (and cellular responses) in exposed (survived) individuals that correlate with "protective immunity".

Avian vaccines under development and in phase I-III trials

- Avian vaccines currently under development include:
- Inactivated vaccines: whole virus (H5N1, H9N2, H2N2); split virus (H5N3, H5N1, H2N2, H7N1, H7N7, H9N2); and subunit (H5N1)
- Recombinant subunit vaccines: HA, M2e, VLP
- Plasmid DNA (HA plus internal genes)
- Live attenuated, cold-adapted vaccines
- Unadjuvanted vs. adjuvanted vaccines: alum, MF59, AS03, TLR ligands have been used as adjuvants
- The immunological parameters followed in clinical trials include HAI (using horse RBC) and microneutralization assays the principal surrogate measure of efficacy is HAI antibody titer. The endpoint criteria are based on the seasonal influenza vaccines:
- ***Seroconversion***- % subjects with a minimum 4-fold rise in HAI titer in >40% (<65)/ >30% ($\geq$ 65)
- ***Seroprotection***- % subjects with titer > 1:40 in $\geq$70% / $\geq$60% (<65/ $\geq$65 yr)
- The above criteria are based upon the assumption of correlation with reduction in influenza-like illness when most of the vaccinated population has some degree of pre-existing immunity against inter-pandemic strains. *This may not be valid for pandemic influenza vaccines.*

Session III. Assays to evaluate vaccine immunogenicity
(chair: Maria Zambon, speakers: John Wood, Guus Rimmelzwaan, Gary Nabel, Maryna Eichelberger, Hana Golding, Walter Gerhard, and Janet McElhaney)
This session included discussion of the assays that are currently available for evaluation of vaccine responsiveness and their limitations. Novel *in vitro* assays were also described.

Immunogenicity of avian influenza vaccines: limitations of current serologic assays

- Hemagglutination inhibition (HAI) assay: HAI for evaluation of seasonal influenza antibodies is based on agglutination of chicken or turkey RBC. This assay is not sensitive for measuring anti-H5 or anti-H7 antibodies due to differences in their receptor binding specificities. Use of horse RBC in the HAI test provides an alternative for the traditional HAI. This assay needs standardization.
- Virus microneutralization assay (VN): this assay utilizes MDCK cells which are sensitive to infection with diverse strains of influenza, including avian influenza viruses of all clades. Comparison of the Horse HAI and VN assays with antibodies against clade 1 and clade 2 avian influenza viruses showed good correlation when a positive microneutralization titer was defined as $\geq$ 1:80.
- Single Radial Haemolysis assay (SRH) is currently used in limited numbers of labs. SRH titer of 25 mm^2 relates to 50% protection against seasonal influenza. The SRH assay may detect antibodies to virus internal proteins and is subject to variability associated with complement, erythrocytes, and source of virus. Applicability for measuring anti-H5 antibodies is lacking.
- Pseudovirion reporter gene based assays are currently under development and demonstrate good sensitivity for measurements of anti-H5N1 antibodies. These assays need further development and side-by-side comparison with the more established assays.
- Neuraminidase enzyme inhibition (NAI) assay: While NA antibodies contribute to protection, the NA content of vaccines and antibody responses to NA are not regularly assessed. The current NAI assay is laborious, uses toxic chemicals, requires large sample size, and is not suitable for automation. Efforts are underway to develop a "micro NAI" that allows large numbers of samples to be analyzed.
- Whole Genome Phage display libraries expressing large confirmation-sensitive epitopes from several avian influenza viruses were generated at CBER. They will be used to identify the breadth of antibody repertoire elicited by different vaccine candidates and in exposed individuals
- *WHO has initiated a collaborative study to evaluate H5N1 serological techniques and to establish an international standard for H5N1 antibody:* Seventeen participating laboratories including NIBSC, CDC, CBER, and NIAID have received test sera, RG H5N1 viral stocks (A/Vietnam/1194/04, A/turkey/Turkey/1/05, A/Anhui/05) along with

reference serum standards (from sheep and vaccine recipients) and SOPs from NIBSC.

Session IV. Correlates of protection against avian influenza: potential insights from humans and animal studies
(chair: Kanta Subbarao, speakers: Jacqueline Katz, Kanta Subbarao, Suzanne Epstein, John Treanor, and Jerry Weir)
This session included presentations on the evaluation of vaccine immunogenicity and efficacy in animal models, heterosubtypic immunity, challenge studies in humans, and the potential use of surrogate measures of efficacy.

Evaluation of vaccine efficacy in animal models and humans

- **Mice**: Some avian influenza viruses, including HP H5N1 viruses replicate efficiently and cause disease without prior adaptation; not all avian influenza strains are lethal. Intranasal infection under anesthesia results in viral pneumonia. Clinical signs include ruffled fur, hunching, labored breathing, hypothermia, weight loss, and mortality.
- Vaccine efficacy in mice was evaluated by examination of disease signs and viral pathogenesis (lung pathology, virus titers in lungs, noses and other tissues) following challenge with wild-type virus. Mice have been immunized with inactivated vaccines at doses ranging from 1 to 10 □g; doses of live virus vaccines range from 10^5-10^6 $TCID_{50}$. Plasmid DNA vaccines have been tested extensively. A dose response was observed with enhanced immunogenicity when adjuvanted TIV vaccines were administered. Vaccination with live attenuated avian influenza vaccines resulted in significant protection in the absence of high neutralizing antibody titers. Mice are a good model for passive transfer of antibodies in order to establish minimal protective levels. Several human monoclonal antibodies against H5N1/Vietnam provide protection against both homologous (the parent wild type virus) and heterologous (different clades) strains of highly pathogenic H5N1 viruses.
- **Ferrets**: Ferrets are naturally susceptible to both human and avian influenza viruses. Multiple parameters can be used to assess vaccine-induced protection: survival; weight loss, fever, lethargy, and kinetics of virus replication in URT (nasal washes) and in the lungs. Studies have used ferrets immunized with 2 doses of 7 to 15 µg inactivated vaccine or a single dose with adjuvant; live virus vaccines have used inoculations of 10^7 $TCID_{50}$ in 0.2 ml. It is difficult to reduce early virus replication in the upper respiratory tract of ferrets even in the presence of a strong serum antibody response; the effect of vaccine is to reduce pulmonary viral replication and enhance clearance. Protection from death is not an optimal parameter; protection against homologous and heterologous challenge strains is best assessed by determining reduction of virus replication.
- Other animal models: Hamsters, guinea pigs, cotton rats, cats and non-human primates have been used as models for influenza pathogenesis

and immunity, providing potential models for study of vaccine-induced protection against highly pathogenic avian viruses.

- Human studies: Seasonal vaccine efficacy and correlates of immunity have been evaluated by comparing virus replication and signs of illness in vaccinated and non-vaccinated individuals following natural infection, or after challenge with wild-type (adults) or attenuated (children) virus strains. These studies have limitations due to expense of safety screening, virus challenge preparations, the absence of information on viral replication and pathogenesis in the lower respiratory tract, and the lack of virulence of recent viruses in adults even when individuals are seronegative. *Not likely to be applicable for avian influenza*
- Surrogate markers of vaccine efficacy: There is a need to correlate protection with both quantitative and qualitative measures of different immune mediators. This can include established end-points (HAI as the gold-standard, virus neutralization titers) as well as new immune parameters (e. g. NA inhibition titers, cell-mediated responses).

Panel Discussion and general recommendations of workshop participants
(panelists: Robert Couch, Jacqueline Katz, Maria Zambon, Kanta Subbarao, Bob Bleshe, Ed Kilbourne, Wendy Keitel, and Peter Wright)
The meeting concluded with a panel discussion that addressed issues that had been raised during the sessions and discussed approaches to expedite the evaluation of pandemic vaccines.

1. In order to facilitate the standardization of key laboratory assays to evaluate vaccine responsiveness and heterotypic viral neutralization, there is an immediate need for production of reference standard reagents including low pathogenic avian viral stocks, positive immune sera (from animals and humans) and common SOPs.
2. For measurement of cellular responses reagents (e.g. high quality peptide pools) and implementation of reproducible standardized assays are needed
3. Novel assays need to be developed to measure mucosal immunity, NA inhibition antibody titers and for better identification of protective (conserved) epitopes.
4. The mouse model is useful for large proof-of-concept studies and for comparison of vaccine formulations and novel adjuvants. There are many advantages to using this model: multiple reagents are available for evaluation of both humoral and cellular immune responses; mechanisms of protection can be identified by transfer of immune cells and sera from vaccinated mice to naïve animals; immunohistochemistry and histopathology provide valuable information.
5. Vaccines undergoing clinical evaluation may benefit from parallel studies in ferrets using the same formulations and dose range.

Development of reagents to allow measurement of cell-mediated responses in the ferret is a priority. Challenge with homologous and heterologous avian influenza strains (i.e. the same or different clades) could provide important information on the breadth of protection.

6. A more programmatic approach to pandemic vaccine trials, with use of standardized assays and reference reagents may facilitate comparison of clinical trials and expedite vaccine development.

References:

1. [FDA panfluvac guidance]

2. [FDA trifluvac guidance]

3. Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. *Safety and Immunogenicity of an Inactivated Influenza A (H5N10 Vaccine.* N Engl J Med. 2006 Mar 30; 354(13):1343-51.

4. [FDA] *Establishing a docket for the development of safety and effectiveness assessments of vaccines used for pandemic influenza.* Federal Register 2007 Oct 4;72(192):56772-56773

5. Expert Committee on Biological Standardization. *Proposed Guidelines: Regulatory Preparedness for Human Pandemic Influenza Vaccines.* World Health Organization, ECBS Meeting, Geneva, 8-12 Oct. 2007

6. Celis, P. *Overview of Regulatory Requirements in Europe.* European Medicines Agency (EMEA), 26 Nov 2007

7. Stephenson I, Nicholson KG, Wood JM, Zambon MC, and Katz JM. *Confronting the avian influenza threat: vaccine development for a potential pandemic*. Lancet Infect Dis. 2004 Aug;4(8):499-509.

* Stephenson I, Bugarini R, Nicholson KG, Podda A, Wood JM, Zambon MC. *Cross-reactivity to highly pathogenic avian influenza H5N1 viruses after vaccination with nonadjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a potential priming strategy.* Infect Dis. 2005 Apr 15;191(8):1210-5. Epub 2005 Mar 14.

* Ohmit SE, Victor JC, Rotthoff JR, Teich ER, Truscon RK, Baum LL, Rangarajan B, Newton DW, Boulton ML, Monto AS. *Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines.* N Engl J Med. 2006 Dec 14;355(24):2513-22.

Appendix III:
Guidance to Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

Guidance for Industry

Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Product Applications at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
MAY 2007

Table of Contents

I. INTRODUCTION.....22
II. BACKGROUND.....23
III. CLINICAL DATA TO SUPPORT THE LICENSURE OF PANDEMIC INFLUENZA VACCINES.....24
A. Approval of a Pandemic Influenza Vaccine for Manufacturers of a U.S. Licensed Seasonal Inactivated Influenza Vaccine where the Process for Manufacturing the Pandemic Influenza Vaccine is the Same.....25
1. Immunogenicity.....25
2. Safety.....26
3. Pediatrics.....26
4. Postmarketing Information.....26
B. Approval of a Pandemic Influenza Vaccine for Manufacturers of a U.S. Licensed Seasonal Live Attenuated Influenza Vaccine where the Process for Manufacturing the Pandemic Influenza Vaccine is the Same.....27
1. Immunogenicity.....27
2. Safety.....28
3. Postmarketing Information.....28
C. Accelerated Approval of a Pandemic Influenza Vaccine Manufactured by a Process not U.S. Licensed.....29
1. Effectiveness.....30
2. Safety.....32
3. Postmarketing Confirmatory Studies.....32
4. Postmarketing Information.....33
D. Additional Considerations.....33
1. Types of Pandemic Influenza Vaccines.....33
2. Clinical Lot Consistency.....33
3. Adjuvanted Pandemic Vaccines.....34
4. Alternative Routes of Administration.....35
5. Investigating Schedules for Administration for Use Prior to Pandemic….....……...……...……..35
6. Pediatric Research Equity Act.....35
7. Postmarketing Evaluations.....36
IV. REFERENCES.....37

Guidance for Industry

Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document is intended to provide to you, sponsors of pandemic influenza vaccines, guidance on clinical development approaches to facilitate and expedite the licensure of influenza vaccines where the intended indication is for active immunization in persons at high risk of exposure to, or during a pandemic caused by, pandemic influenza viruses. We, FDA, also discuss pursuing licensure of an influenza vaccine for indication and usage during the prepandemic stage in Section III.D.5. – Investigating Schedules for Administration for Use Prior to a Pandemic. The approaches in this guidance apply to both nonadjuvanted and adjuvanted hemagglutinin-based pandemic vaccines, including "split virus," subunit, and whole virus inactivated vaccines propagated in embryonated chicken eggs or cell-culture, and to recombinant hemagglutinin-based protein vaccines, and DNA vaccines that express hemagglutinin. We also address live attenuated influenza vaccines. This document does not address influenza vaccines that do not rely on immunity to a hemagglutinin component.

This document does not address the nonclinical development of investigational vaccines. Successful nonclinical evaluation is an important step before proceeding with clinical development (Ref. 1). This document also does not address the chemistry, manufacturing, control, or inspection of the manufacturing facility needed for licensure. These aspects of the license application are addressed in the guidance document entitled, "Guidance for Industry: Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for a Vaccine or Related Product." 1 Applicants may contact the Center for Biologics Evaluation and Research (CBER) for additional information about these aspects of vaccine development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

[1] See http:// www.fda.gov/cber/vaccine/vacpubs.htm .

[2] For information on the number of confirmed clinical cases due to H5N1 strains, see the World Health Organization's website: www.who.int/csr/disease/avian_influenza/country/en/index.html.

[3] See http://www.fda.gov/cber/vaccine/vacpubs.htm .

[4] CBER has prepared similar guidance for seasonal influenza vaccines. See "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines" (http://www.fda.gov/cber/vaccine/vacpubs.htm).

II. BACKGROUND

Influenza viruses are enveloped ribonucleic acid viruses belonging to the family of *Orthomyxoviridae* and are divided into three distinct types on the basis of antigenic differences of internal structural proteins (Ref. 2). Two influenza types, Type A and B, are responsible for yearly epidemic outbreaks of respiratory illness in humans and are further classified based on the structure of two major external glycoproteins, hemagglutinin (HA) and neuraminidase (NA). Type B viruses, which are largely restricted to the human host, have a single HA and NA subtype. In contrast, numerous HA and NA Type A influenza subtypes have been identified to date. Type A strains infect a wide variety of avian and mammalian species.

Type A and B influenza variant strains emerge as a result of frequent antigenic change, principally from mutations in the HA and NA glycoproteins. These variant strains may arise through one of two mechanisms: selective point mutations in the viral genome (Refs. 3 and 4) or from reassortment between two co-circulating strains (Refs. 5 and 6).

Since 1977, influenza A virus subtypes H1N1 and H3N2, and influenza B viruses have been in global circulation in humans. The current U.S. licensed trivalent vaccines are formulated to prevent influenza illness caused by these influenza viruses (Ref. 7).

Pandemic influenza outbreaks have occurred when a new Type A hemagglutinin subtype emerges to which the population has not been exposed and has little or no immunity. During the twentieth century, three pandemic influenza outbreaks occurred. Pandemic influenza strains can evolve following genetic reassortment of two co-circulating viruses, one of which originates from an animal reservoir and one from human origin. Such a reassortment led to the emergence of the 1957 H2N2 subtype pandemic strain and the 1968 H3N2 subtype pandemic strain. Recent research suggests that the 1918-1919 H1N1 subtype pandemic strain likely resulted from a series of genetic mutations in multiple genes in an influenza strain of avian origin. These mutations appear to have allowed the virus to adapt to and spread among humans (Refs. 8, 9, and 10). The 1918-1919 H1N1 pandemic strain, the most lethal of the twentieth century, resulted in about 50 million deaths worldwide (Ref. 11). The genetic sequencing, phylogenetic analysis and reconstruction of the

1918-1919 H1N1 pandemic strain have provided important insights into virulence factors of influenza viruses (Refs. 9 and 10).

In recent years, human infections with avian influenza viruses have led to increasing concern that one or more of these viral strains may evolve into a pandemic viral strain that is able to spread among humans. Several avian subtypes have been recovered from humans with influenza illness. Influenza H7N7, H9N2 and H5N1 subtype strains have caused disease in humans (Refs. 12, 13, 14, and 15). Of these, the H5N1 strains have raised particular concern. Strains of this subtype are highly virulent with a mortality rate of approximately 50 percent among confirmed clinical cases. The first documented human H5N1 infections occurred in Hong Kong in 1997 in 18 individuals, 6 of whom died. While only rare cases of possible human-to-human transmission have occurred to date (Refs. 16 and 17), the number of human infections continues to increase, and analysis of H5N1 strains isolated from more recent human infections has shown that the virus continues to mutate and that new variants have emerged.2 Of additional concern, recent H5N1 strains are more lethal in animal models, and the host range for H5N1 strains has expanded into mammalian species previously thought to be resistant to avian strains. These events have highlighted the need to develop criteria to evaluate the safety and effectiveness of influenza vaccines directed against potential pandemic strains.

III. CLINICAL DATA TO SUPPORT THE LICENSURE OF PANDEMIC INFLUENZA VACCINES

Licensure of pandemic influenza vaccines may be sought through the submission of a Biologics License Application (BLA) in accordance with either the provisions in 21 CFR 601.2 or the accelerated approval provisions in 21 CFR Part 601 Subpart E. This Section provides recommendations for clinical data needed to support such approvals for pandemic influenza vaccines. CBER has prepared similar guidance for seasonal influenza inactivated vaccines, Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Influenza Vaccines.3

Biological products are licensed under the authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). Under section 351, BLAs are approved only upon a showing that the product is "safe, pure and potent," and that the manufacturing facility meets standards designed to assure that the biological product "continues to be safe, pure, and potent." In previously issued guidance entitled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" dated May 1998 (section II.A.), FDA stated, "*Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for 'adequate and well-controlled studies' for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25(d)(2))."

A. Approval of a Pandemic Influenza Vaccine for Manufacturers of a U.S. Licensed Seasonal Inactivated Influenza Vaccine where the Process for Manufacturing the Pandemic Influenza Vaccine is the Same

If a manufacturer holds a U.S. license for an approved BLA for a seasonal inactivated influenza vaccine under either the provisions in 21 CFR 601.2 or the accelerated approval provisions with the vaccine's clinical benefit having been confirmed in a postmarketing study, and the manufacturing process used for the production of the pandemic vaccine is the same as for the licensed product, clinical immunogenicity trials
would be needed to determine the appropriate dose and regimen of a pandemic influenza vaccine candidate. These trials should also include an assessment of safety. Sponsors can expect that we will seek their involvement on plans to collect additional effectiveness and safety information when the vaccine is used (see Section III.A.4., below).

All submissions for the initial licensure of a pandemic influenza vaccine should be submitted as BLAs, which will provide for a trade name and labeling specific to the pandemic vaccine. For sponsors with existing licensed seasonal inactivated influenza vaccines who intend to file a BLA for a pandemic influenza vaccine that utilizes the same manufacturing process, we would expect that the BLA would reference the original BLA, including the nonclinical and chemistry, manufacturing, and controls (CMC) data in their original BLA.

1. Immunogenicity

Data to support the selected dose and regimen should be based on the evaluation of immune responses elicited by the vaccine. The hemagglutination inhibition (HI) antibody assay has been used to assess vaccine activity and may be appropriate for the evaluation of the pandemic influenza vaccine. Appropriate endpoints may include: 1) the percentage of subjects achieving an HI antibody titer $\geq$ 1:40, and 2) rates of seroconversion, defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post vaccination HI titer $\geq$ 1:40 or a pre-vaccination HI titer $\geq$ 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer. In a prepandemic setting it is likely that most subjects will not have been exposed to the pandemic influenza viral antigen(s). Therefore, it is possible that vaccinated subjects may reach both suggested endpoints. Thus, for studies enrolling subjects who are immunologically naïve to the pandemic antigen, one HI antibody assay endpoint, such as the percentage of subjects achieving an HI antibody titer $\geq$ 1:40, may be considered. Point estimates and the two-sided 95% confidence intervals (CI) of these evaluations should be provided with the BLA. The geometric mean titers (GMT) at pre- and post-vaccination should also be included.

Considerable variability can be introduced into the laboratory assay used to measure HI antibodies as a result of a number of factors including differences in viral strains and red blood cell types, and the presence of non-specific inhibitors in the assay medium. Thus, suitable controls and assay validation are important for interpreting HI antibody results. It is also recommended that adequate serum sample volumes be obtained and stored for possible later use in confirmatory or comparative assay studies, if needed.

Other endpoints and the corresponding immunologic assays, such as the microneutralization assay, might also be used to support the approval of a pandemic influenza vaccine BLA (Ref. 18). Sponsors are encouraged to discuss their proposals with CBER early in development.

2. Safety

Local and systemic reactogenicity should be well defined in all age groups for whom approval of the vaccine is sought. Appropriate grading scales to describe the severity of the adverse events should be included in the study protocol. Serious adverse events must be monitored and collected for all subjects throughout the duration of the studies (21 CFR 312.23, 312.32, 312.56, 312.60 and 312.62). The protocol should include a clinic visit or telephone contact at least six months post-vaccination to ascertain additional serious adverse events and new onset of chronic illnesses that may have occurred in the interim. Safety data gathered from the six month post-vaccination evaluation must be submitted to FDA (21 CFR 312.32 and 312.33). This may occur after submission or approval of the BLA. Sponsors are encouraged to initiate an early dialogue with CBER to reach agreement on the size of the safety database needed to support product licensure. This is especially true when there is minimal postmarketing experience with the U.S. licensed seasonal influenza vaccine, such as immediately after licensure of a vaccine manufactured with a new adjuvant or using a new process.

3. Pediatrics

It is anticipated that data will be collected in adults and in the pediatric population in a step-wise fashion. We assume that approval for use in the adult population, including the geriatric population, would be sought with the initial application. The amount of data needed for a particular sponsor's pandemic influenza vaccine to support approval for use in the pediatric population will depend on available clinical data for that sponsor's U.S. licensed seasonal influenza vaccine. The timing of the clinical development in the pediatric population warrants discussion with CBER. Please refer to Section III.D. – Additional Considerations, paragraph 6, for a discussion of the Pediatric Research Equity Act (PREA).

4. Postmarketing Information

All sponsors who seek licensure of a pandemic influenza vaccine 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. Sponsors may indicate their intent in their BLA's postmarketing surveillance plans.

B. Approval of a Pandemic Influenza Vaccine for Manufacturers of a U.S. Licensed Seasonal Live Attenuated Influenza Vaccine where the Process for Manufacturing the Pandemic Influenza Vaccine is the Same

As for inactivated pandemic influenza vaccines discussed in Section III.A. above, clinical trials to determine the appropriate dose and regimen of a live attenuated pandemic influenza vaccine would be needed and should include an assessment of immunogenicity and safety. Sponsors can expect FDA to seek their involvement in plans to collect additional effectiveness and safety information, such as through epidemiological studies, should a pandemic influenza situation be declared or if use occurs in persons at high risk of exposure to the virus.

Sponsors with licensed seasonal live attenuated influenza vaccines who intend to seek licensure for a pandemic influenza vaccine that utilizes the same manufacturing process should submit a new BLA, which will provide for a trade name and labeling specific to the pandemic vaccine. We would expect that the new BLA would reference the BLA for the seasonal vaccine, including the nonclinical and CMC data in their original BLA.

1. Immunogenicity

Data to support the selected dose and regimen should be based on the evaluation of immune responses elicited by the vaccine. Live attenuated influenza vaccine may elicit a variety of immune responses, and the HI antibody response may be appropriate for the evaluation of the new pandemic influenza vaccine strain, helping to bridge its observed immunogenicity to seasonal vaccines for which clinical efficacy has been demonstrated. However, live attenuated influenza vaccines may induce protection against disease through immunological mechanisms other than, or in addition to, HI antibodies. Thus, sponsors may propose alternative endpoints for our consideration. For the HI antibody assay, we recommend the following endpoints: 1) the percentage of subjects achieving an HI antibody titer $\geq$ 1:40, and 2) rates of seroconversion, defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post vaccination HI titer $\geq$ 1:40 or a pre-vaccination HI titer $\geq$ 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer. In a prepandemic setting it is likely that most subjects will not have been exposed to the pandemic antigen(s). Therefore, it is possible that vaccinated subjects may reach both suggested endpoints. Thus, for studies enrolling subjects who are immunologically naïve to the pandemic influenza virus antigen(s), one HI antibody assay endpoint, such as the percentage of subjects achieving an HI antibody titer $\geq$ 1:40, may be considered. Point estimates and the two-sided 95%

CIs of these evaluations should be provided with the BLA. The GMTs at pre- and post-vaccination should also be included.

2. Safety

Clinical studies with live attenuated influenza pandemic vaccines performed in advance of a pandemic influenza outbreak present special considerations. Therefore, sponsors are encouraged to initiate an early dialogue with CBER to agree on the size of the safety database needed to support product licensure.

Subjects should be isolated during the study period to minimize the potential for transmission of the influenza vaccine viral strain. The amount and duration of vaccine shedding should be well characterized from all subjects. Contact precautions should be in place for study subjects and study personnel for the duration of shedding. Study personnel should be monitored for possible influenza illness and transmission of the influenza vaccine strain. Study subjects and study personnel with symptoms suggestive of influenza illness should be treated with antiviral agents pending culture or other microbiological results.

Local and systemic reactogenicity events and symptoms of influenza illness should be well defined in all age groups for whom approval of the vaccine is sought. Appropriate grading scales to describe the severity of the adverse events should be included in the study protocol. Serious adverse events must be monitored and collected for all subjects throughout the duration of the studies (21 CFR 312.23, 312.32, 312.56, 312.60 and 312.62). The protocol should include a clinic visit or telephone contact at least six months post-vaccination to ascertain additional serious adverse events and new onset of chronic illnesses that may have occurred in the interim. Safety data gathered from the six month post-vaccination evaluation must be submitted to FDA (21 CFR 312.32 and 312.33). This may occur after submission or approval of the BLA.

Because of theoretical concerns for reassortment between a live attenuated pandemic influenza vaccine strain and other circulating influenza strains, a live attenuated pandemic vaccine might be indicated for use only after the onset of a pandemic influenza outbreak. Any plans to develop such products for potential use in a prepandemic setting, in particular the size of the safety database required to support such use, should be discussed with CBER.

3. Postmarketing Information

All sponsors who seek licensure of a pandemic influenza vaccine 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. Sponsors may indicate their intent in their BLA's postmarketing surveillance plans.

C. Accelerated Approval of a Pandemic Influenza Vaccine Manufactured by a Process not U.S. Licensed

Accelerated approval may be granted for certain biological products such as pandemic influenza vaccines that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments. For pandemic vaccines, the accelerated approval pathway will be available at least until adequate supplies of such vaccines are available. (See Accelerated Approval of Biological Products for Serious or Life Threatening Illnesses (21 CFR 601 Subpart E)).

Such an approval will be based on adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit (21 CFR 601.41). Approval under this section will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit (21 CFR 601.41). Postmarketing studies must also be adequate and well-controlled and should be conducted with due diligence (21 CFR 601.41). The protocols for these studies should be submitted with the original BLA. Marketing approval for biological products approved under these regulations may be withdrawn, for example, if the postmarketing clinical study fails to verify clinical benefit or the sponsor fails to perform the required postmarketing study with due diligence (21 CFR 601.43(a)(1) and (2)).

For pandemic influenza vaccines, the immune response elicited following receipt of the vaccine may serve as a surrogate endpoint that is likely to predict clinical benefit, that is, prevention of influenza illness and its complications. Influenza virus hemagglutinins, present on viral surfaces, are important for cell-receptor binding. The immune response to these hemagglutinins as measured by the presence of serum HI antibodies is an important protective component following vaccination and/or infection.

To date, prospectively designed studies to evaluate the effectiveness of influenza vaccines have not identified a specific HI antibody titer associated with protection against culture-confirmed influenza illness. Some studies of influenza infection, including human challenge studies following vaccination, have suggested that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects and that protection from illness is increased with higher titers (Refs. 19 and 20). Evaluations of seroconversion and GMT have been used as measures of vaccine activity (Refs. 21 and 22).

For the purposes of accelerated approval of inactivated pandemic influenza vaccines, the HI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. Currently immune

response data following receipt of live attenuated influenza vaccines are limited. Accelerated approval of new live attenuated pandemic influenza vaccines will depend on the identification of an immune surrogate that is reasonably likely to predict clinical benefit.

To be considered for accelerated approval, a BLA for a pandemic inactivated influenza vaccine should include results from one or more adequate and well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory postmarketing studies. In addition, all sponsors who seek licensure of a pandemic influenza vaccine through accelerated approval should expect FDA to seek their involvement in working with FDA and other governmental agencies on plans to collect additional effectiveness and safety information, such as through epidemiological studies, when the vaccine is used. Since each vaccine candidate is unique (e.g., particular product characteristics, manufacturing process, etc.), we recommend that you discuss with CBER early in development the adequacy of the manufacturing methods and product testing and the extent of the clinical data needed to license your candidate vaccine.

1. Effectiveness

This Section describes possible approaches for establishing effectiveness based on immune responses under an accelerated approval. Because our understanding of immune responses to various possible pandemic strains is evolving, the effectiveness criteria stated below are current recommended targets. We are open to considering other study designs, other surrogate endpoints reasonably likely to predict benefit, along with other proposed performance targets for the surrogate endpoints described below or for other surrogate endpoints.

a. A placebo-controlled immunogenicity trial in which HI antibody responses to the new vaccine are assessed may be supportive of accelerated approval if the study was adequately powered to assess the co-primary endpoints: 1) seroconversion rates, and 2) percentage of subjects achieving an HI antibody titer ≥ 1:40. In a prepandemic setting it is likely that most subjects will not have been exposed to the pandemic influenza viral antigen(s). Therefore, it is possible that vaccinated subjects may reach both suggested endpoints. Thus, for studies enrolling subjects who are immunologically naïve to the pandemic influenza antigen, one HI antibody assay endpoint, such as the percentage of subjects achieving an HI antibody titer ≥ 1:40, may be considered.

For example, the following, which have been modified from guidelines by the currently-titled, "Committee for Medicinal Products for Human Use of the European Medicines Agency" (Ref. 21), may support an accelerated approval of seasonal inactivated vaccines.4 The following may be used as a guide in developing endpoints that would support accelerated approval of pandemic influenza vaccines.

For adults < 65 years of age and for the pediatric population:

- The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.

- The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.

For adults ≥ 65 years of age:

- The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%.

- The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.

b. If a U.S. licensed pandemic influenza vaccine exists against a strain for which the sponsor is seeking licensure of a new vaccine, a non-inferiority comparison, as assessed by HI antibody responses, to the U.S. licensed pandemic influenza vaccine may support accelerated approval. The study should be adequately powered to assess the co-primary endpoints: 1) GMT, and 2) seroconversion rates.

For the co-primary endpoints consider the following:

- The upper bound of the two-sided 95% CI on the ratio of the GMTs ($GMT_{\text{U.S. licensed vaccine}}/GMT_{\text{new vaccine}}$) should not exceed 1.5. A proposal for use of a different GMT ratio should be based upon the characteristics of the assay that will be used to assess antibody responses.

- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates ($\text{Seroconversion}_{\text{U.S. licensed vaccine}} - \text{Seroconversion}_{\text{new vaccine}}$) should not exceed 10 percentage points.

c. Alternative study designs that assess different endpoints and/or other immune responses will be reviewed by CBER and may be accepted in support of an accelerated approval. CBER would need to determine that the study design is acceptable and the proposed surrogate endpoint(s) is reasonably likely to predict clinical benefit.

2. Safety

Safety data must be collected from subjects enrolled in pre-licensure clinical trials intended to support the accelerated approval of a pandemic vaccine (21 CFR 312.23, 312.32, 312.56, 312.60 and 312.62). The monitoring of these subjects should follow the outline described in Section III.A.2. above. The data gathered six months post-vaccination evaluation should be submitted to FDA at the time of the BLA submission. In addition, safety laboratory tests, including hematologic and clinical chemistry evaluations, should be obtained pre- and post-vaccination at least in the first clinical study(ies). These may be needed in other studies, depending on the initial clinical studies and pre-clinical data. A total safety database large enough to rule out a serious adverse event that occurs at a rate of 1 in 300 may be sufficient when a sponsor has adequate marketing and safety experience with the same manufacturing process for a seasonal vaccine licensed outside the United States and these data are presented in the BLA and assessed as such. For example, the upper limit of the two-sided 95% CI of the true serious adverse event rate is 0.0032 (<1 in 300) when no serious adverse event is observed among 1150 subjects who received vaccine in the clinical trials, using the Clopper-Pearson method. However, the size of the pre-licensure safety database, especially for vaccines manufactured using novel processes, such as cell-culture, and for pandemic vaccines that contain novel adjuvants, would be influenced by factors such as the nature of the new manufacturing process and available preclinical and clinical data and should be discussed with CBER. Moreover, if a serious adverse event is present in a safety database of about 1,000 subjects, and there is concern that it may be vaccine-related, then additional safety data may be needed. Safety data to support use in pediatric populations would also be needed and should be submitted either as part of the BLA or as a clinical efficacy supplement at a later time, if pediatric studies are deferred under PREA. Please refer to Section III.D. – Additional Considerations, paragraph 6, for a discussion of the Pediatric Research Equity Act (PREA).

3. Postmarketing Confirmatory Studies

There may be other approaches to fulfilling the postmarketing confirmatory study requirement to demonstrate clinical benefit under 21 CFR 601.41 than those recommended below. Sponsors are encouraged to discuss their plans with CBER.

a. Confirmatory studies if a sponsor pursues U.S. licensure of a seasonal vaccine

Sponsors seeking approval of a pandemic influenza vaccine strain may also choose to pursue development and licensure of a seasonal influenza vaccine using the same manufacturing process as used for the pandemic influenza vaccine (see footnote 4). Approval of the seasonal vaccine, other than through accelerated approval, may help fulfill the postmarketing requirement to verify the clinical benefit of the pandemic influenza vaccine.

b. Confirmatory studies if a sponsor does not pursue U.S. licensure of a seasonal

influenza vaccine

Other approaches to demonstrating clinical benefit may be possible and sponsors desiring to pursue these other approaches should discuss their plans with CBER as soon as possible.

4. Postmarketing Information

All sponsors who seek licensure of a pandemic influenza vaccine, including those granted accelerated approval under 21 CFR 601.41, 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. Sponsors may indicate their intent in their BLA's postmarketing surveillance plans.

D. Additional Considerations

1. Types of Pandemic Influenza Vaccines

The recommendations in Section III.C. above, regarding clinical data to support the accelerated approval of a pandemic vaccine, apply to both nonadjuvanted and adjuvanted hemagglutinin-based pandemic vaccines, including "split virus," subunit, and whole virus inactivated vaccines propagated in embryonated chicken eggs or cell-culture, and to recombinant hemagglutinin-based protein vaccines, and DNA vaccines that express hemagglutinin. Detailed information on product characteristics and manufacturing processes are needed for all new vaccines, regardless of their derivation (see footnote 1).

2. Clinical Lot Consistency

The objective of a clinical lot consistency study is to show consistency of manufacturing and performance of the final product by demonstrating that three consecutively manufactured final formulated bulk lots of vaccine elicit equivalent immune responses. The HI antibody assay may be used to assess the immune responses. We recommend a pair-wise comparison of the 95% CI on the ratio of GMTs for the viral strain contained in the three vaccine lots as an appropriate primary endpoint. The two-sided 95% CI on the GMT ratio should be entirely within 0.67 and 1.5. Seroconversion rates for the HI antibody response for the viral strain contained in the vaccine may be assessed as secondary endpoints. Assessment of lot consistency may be incorporated in studies designed to support the accelerated approval of a new influenza vaccine. We may decide, on a case by case basis that lot consistency may be evaluated and incorporated in the postmarketing commitment studies. This determination would be influenced by factors such as the manufacturing process used for the pandemic influenza vaccine and available manufacturing and clinical experience.

3. Adjuvanted Pandemic Vaccines

Small studies of inactivated nonadjuvanted pandemic influenza vaccines have shown that more antigen per dose and more than one dose are likely to be needed to elicit immune responses comparable to those elicited following a single dose of an annual seasonal inactivated influenza vaccine (Ref. 23). An effective adjuvant might reduce the amount of antigen needed to elicit protective immune responses and may also have other desirable properties, such as cross protection against evolving strains and priming the immune system in a prepandemic setting.

Data supporting the safety of the adjuvanted formulation and the added benefit over the unadjuvanted formulation must be submitted in the BLA (42 U.S.C. 262(a)(2)(C)(i); 21 CFR 601.2). At an early stage of development, clinical data supporting the value of adding the adjuvant should be provided, such as evidence of enhanced immune response, antigen-sparing effects, or other advantages, as should data supporting selection of the dose of the adjuvant itself. Safety information in the BLA may include the safety experience obtained from domestic or foreign trials. Safety experience from the same adjuvant formulated with other vaccine antigens may also contribute to the adjuvant's safety evaluation. It is expected that nonclinical and clinical information needed to support the safety of the adjuvant be discussed with us early in development. Finally, to delineate additional information about the adjuvanted vaccine's safety profile, we may seek agreement from sponsors to conduct certain postmarketing studies.

- Dose and Formulation Selection

Assuming that the vaccine is a hemagglutinin-based product, the HI antibody assay may be appropriate to evaluate the immune response.

For initial dose and formulation selection, a comparative clinical study of adjuvanted vs. non-adjuvanted vaccines that both contain the same amount of antigen should demonstrate that the immune response elicited by the adjuvanted antigen is better than that elicited by the same antigen alone. For differences in HI antibody titer and seroconversion rates, the lower confidence limit on the appropriate point estimate excluding equality (i.e., the value 1 for the ratio parameter or 0 for the difference parameter) may be sufficient to demonstrate the added value of the adjuvant.

A comparative study of an adjuvanted vaccine containing a lower amount of antigen than the dose-optimized non-adjuvanted vaccine formulation may be conducted to demonstrate non-inferior immune responses elicited by the adjuvanted vaccine. Other approaches to demonstrate the value of the adjuvant, such as a greater ability of an adjuvanted vaccine to induce antibodies that cross-react with a wider variety of subtypes, strains, or clades, when compared to an unadjuvanted vaccine, may be possible. Sponsors are encouraged to discuss their proposals with CBER.

Selection of an appropriate dose and formulation should also be guided by the safety profile of the formulations and regimens being studied.

4. Alternative Routes of Administration

Alternative routes of influenza vaccine administration (e.g., transdermal inoculation by needle or transdermal vaccination using a patch, which may involve the use of novel devices) are being investigated with the goals of reducing the amount of antigen needed to elicit immune responses that are likely to protect against influenza illness and of enhancing ease of vaccinations. Such strategies might expand the available vaccine supply and/or increase the ease and speed of large scale immunization programs. In cases where no novel manufacturing concerns are raised (such as intradermal administration of a pandemic vaccine formulation licensed for intramuscular administration) and the quantity and quality of the vaccine composition remains the same, approval may be possible as a clinical efficacy supplement to a BLA based on clinical immunogenicity and limited safety data. In other cases or when a sponsor is uncertain about the data needed to support licensure of vaccines utilizing novel delivery methods, the sponsor should consult with CBER early in development.

5. Investigating Schedules for Administration for Use Prior to a Pandemic

Different schedules of influenza vaccine administration may also be investigated as a strategy for pandemic preparedness. Studies may involve varying the number and strength of initial doses followed by a subsequent booster dose at different time periods using either homologous or heterologous antigen. Results of these studies may generate information about cross-reactive antibodies induced by novel antigens and may help inform public health decisions about developing potential antigen-sparing strategies. Sponsors are encouraged to consider supplementing their product development pathway to include these studies and to consult with CBER about study design so that these studies could support evaluation and approval for such indications.

6. Pediatric Research Equity Act

The Pediatric Research Equity Act of 2003 (PREA) (Public Law 108-155) addresses drug and biological product development for pediatric uses. All sponsors have obligations to study pediatric populations as outlined in PREA. Under PREA, all applications (or supplements) submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration are to contain a pediatric assessment (pediatric clinical data) unless the sponsor has obtained a waiver or deferral from FDA (21 U.S.C. 355c). A draft guidance on the implementation of PREA was issued by FDA in September 2005 (Ref. 24). As

stated in that document, FDA encourages the submission of pediatric development plans to FDA as early as possible in the vaccine development process to increase understanding of vaccine immunogenicity, dosing, and safety information in the pediatric population. The indication for a pandemic vaccine to be used during a pandemic is relevant for the pediatric population.

7. Postmarketing Evaluations

a. Effectiveness

As discussed in Sections III.A. through C. above, pandemic influenza vaccines may be approved on the basis of immunogenicity data. All sponsors who seek licensure of a pandemic influenza vaccine, including those granted accelerated approval under 21 CFR 601.41, 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. Sponsors may indicate their intent in their BLA pharmacovigilance plans. The additional data may allow a better understanding of the relationship between immunogenicity of the vaccine and clinical effectiveness. As discussed in Section III.C. above, for pandemic influenza vaccines approved under an accelerated approval, sponsors will also need to conduct a postmarketing confirmatory study to verify clinical benefit, and should include their study plans with their application.

b. Safety

As part of the BLA submission, sponsors should include a pharmacovigilance plan in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E2E guidance) (Ref. 25). Special attention should be paid to safety issues that might arise because of novel manufacturing processes and/or novel adjuvants. FDA and the Centers for Disease Control and Prevention plan to conduct enhanced safety surveillance during early use of the vaccine, both prepandemic and during a pandemic. FDA encourages sponsors to work in advance with us to develop safety surveillance strategies to best serve public health during a pandemic including the development and testing of postmarketing pandemic surveillance data gathering, communications, and reporting.

In addition, sponsors who wish to enhance the safety database and safety-related labeling of their pandemic use influenza vaccine may conduct safety studies prior to a pandemic influenza outbreak, for example among individuals identified by public health authorities for prepandemic vaccination.

IV. REFERENCES

1. World Health Organization. WHO guidelines on nonclinical evaluation of vaccines. Annex 1. WHO Technical Report Series. 2005;927:31-63. www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/.

2. Lamb RA, Krug RM. *Orthomyxoviridae*: The Viruses and Their Replication. In: Fields Virology, Editors-in-Chief: Knipe DM and Howley PM. 4th Edition. Philadelphia, PA: Lippincott Williams and Wilkins, Publishers; 2001;1487-1531.

3. Palese P, Garcia-Sastre A. Influenza vaccines: present and future. The Journal of Clinical Investigation. 2002;110:9-13.

4. Nakajima S, Nobusawa E, Nakajima K. Variation in response among individuals to antigenic sites on the HA protein of human influenza virus may be responsible for the emergence of drift strains in the human population. Virology. 2000;274:220-231.

5. Holmes EC, Ghedin E, Miller N, Taylor J, Bao Y, St. George K, Grenfell BT, Salzberg SL, Fraser CM, Lipman DJ, Taubenberger JK. Whole-genome analysis of human influenza A virus reveals multiple persistent lineages and reassortment among recent H3N2 viruses. PLoS Biology. 2005;3:1579-1589.

6. Barr IG, Komadina N , Hurt AC , Iannello P , Tomasov C , Shaw R , Durrant C , Sjogren H , Hampson AW . An influenza A(H3) reassortant was epidemic in Australia and New Zealand in 2003. Journal of Medical Virology. 2005;76:391-397.

7. Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity and Mortality Weekly Report. 2005;54(RR-8):1-40.

8. Reid AH, Fanning TG, Janczewski TA, Lourens RM, Taubenberger JK. Novel origin of the 1918 pandemic influenza virus nucleoprotein gene. Journal of Virology. 2004;78:12462-12470.

9. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. Nature. 2005;437:889-893.

10. Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solorzano A, Swayne DE, Cox NJ, Katz JM, Taubenberger JK, Palese P, Garcia-Sastre A. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science. 2005;310:77-80.

11. Johnson NPAS, Mueller J. Updating the accounts: Global mortality of the 1918-1920 "Spanish" influenza pandemic. Bulletin of the History of Medicine. 2002;76:105-115.

12. Fouchier RAM, Schneeberger PM, Rozendaal FW, Broekman JM, Kemink SAG, Munster V, Kuiken T, Rimmelzwaan GF, Schutten M, van Doornum GJJ, Koch G, Bosman A, Koopmans M, Osterhaus ADME. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proceedings of the National Academy of Sciences of the United States of America. 2004;101:1356-1361.

13. Lin YP, Shaw M, Gregory V, Cameron K, Lim W, Klimov A, Subbarao K, Guan Y, Krauss S, Shortridge K, Webster R, Cox N, Hay A. Avian-to-human transmission of H9N2 subtype influenza A viruses: Relationship between H9N2 and H5N1 human isolates. Proceedings of the National Academy of Sciences of the United States of America. 2000;97:9654-9658.

14. Claas ECJ, Osterhaus ADME, van Beek R, De Jong JC, Rimmelzwaan GF, Senne DA, Krauss S, Shortridge KF, Webster RG. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. The Lancet. 1998;351:472-477.

15. Subbarao K, Klimov A, Katz J, Regnery H, Lim W, Hall H, Perdue M, Swayne D, Bender C, Huang J, Hemphill M, Rowe T, Shaw M, Xu X, Fukuda K, Cox N. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. Science. 1998;279:393-396.

16. Ungchusak K, Auewarakul P, Dowell SF, Kitphati R, Auwanit W,

Puthavathana P, Uiprasertkul M, Boonnak K, Pittayawonganon C, Cox NJ, Zaki SR, Thawatsupha P, Chittaganpitch M, Khontong R, Simmerman JM, Chunsutthiwat S. Probable person-to-person transmission of avian influenza A (H5N1). The New England Journal of Medicine. 2005;352:333-340.

17. Buxton Bridges C, Katz JM, Seto WH, Chan PKS, Tsang D, Ho W, Mak KH, Lim W, Tam JS, Clarke M, Williams SG, Mounts AW, Bresee JS, Conn LA, Rowe T, Hu-Primmer J, Abernathy RA, Lu X, Cox NJ, Fukuda K. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. The Journal of Infectious Diseases. 2000;181:344-348.

18. Rowe T, Abernathy RA, Hu-Primmer J, Thompson WW, Lu X, Lim W, Fukuda K, Cox NJ, Katz JM. Detection of antibody to avian influenza A (H5N1) virus in human serum by using a combination of serologic assays. Journal of Clinical Microbiology. 1999;37:937-943.

19. Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. Journal of Hygiene (Camb). 1972;70:767-777.

20. de Jong JC, Palache AM, Beyer WEP, Rimmelzwaan GF, Boon ACM, Osterhaus ADME. Haemagglutination-inhibiting antibody to influenza virus. Developmental Biology (Basel). 2003;115:63–73.

21. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines. CPMP/BWP/214/96. The European Agency for the Evaluation of Medicinal Products (EMEA), March 1997.

22. Treanor J, Keitel W, Belshe R, Campbell J, Schiff G, Zangwill K, Wolff M, Klimov A, Levandowski R, Lambert L. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. Vaccine. 2002;20:1099-1105.

23. Testimony of Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, on “Pandemic Influenza: The Road to Preparedness” before the Committee on Foreign

Relations, United States Senate, November 9, 2005.

24. FDA Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, September 2005 (http://www.fda.gov/cber/gdlns/pedreseq.htm). This draft guidance, when finalized, will represent FDA's current thinking on that topic.

25. ICH Guidance for Industry: E2E Pharmacovigilance Planning, April 2005 (http://www.fda.gov/cber/gdlns/ichpvp.htm).