

Guidance for Industry

Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

DRAFT GUIDANCE

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For questions on the content of this guidance, contact Antonia Geber, M.D., or Donna Chandler, Ph.D., at 301-827-3070.

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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 for the prevention of disease caused by pandemic influenza viruses. The approaches apply to “split virus” and whole virus inactivated pandemic vaccines propagated in embryonated chicken eggs, and are also applicable to cell-culture derived, recombinant hemagglutinin-based protein, and adjuvanted pandemic influenza vaccines. We, FDA, also address live attenuated influenza vaccines. This document does not address influenza vaccines that do not contain a hemagglutinin component. Current U.S. licensed influenza vaccines are trivalent vaccines approved for the prevention of seasonal influenza illness. Two classes of vaccines are licensed, “split virus” trivalent inactivated vaccines and a live attenuated trivalent vaccine.

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” dated January 1999¹ (64 Federal Register 518, January 5, 1999). Sponsors may contact the Center for Biologics Evaluation and Research (CBER) for additional information about these aspects of vaccine development.

¹ See <http://www.fda.gov/cber/gdlns/cmccvacc.pdf>.

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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, 15 HA and 9 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 epidemic variants may result from one of two mechanisms. They may emerge as a result of selective point mutations in the viral genome (Refs. 3 and 4). Other epidemic variants may evolve from reassortment between two co-circulating strains (Refs. 5 and 6).

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

Pandemic influenza outbreaks occur when a new Type A hemagglutinin subtype emerges to which the population has not been exposed and has little if any 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 viral strain of avian origin. These mutations appear to have allowed the viral strain to adapt to and spread among humans (Refs. 8, 9, and 10). The 1918-19 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 1918-19 H1N1 pandemic strain have provided important new insights into virulence factors of influenza viruses (Refs. 9 and 10).

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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 been of most concern. Strains of this subtype are highly virulent with a mortality rate of approximately 50 percent among confirmed clinical cases. The first documented human infections with H5N1 strains occurred in Hong Kong in 1997 in 18 individuals, 6 of whom died. While only rare documented cases of possible human-to-human transmission have occurred to date (Refs. 16 and 17), H5N1 strains from more recent human infections between 2003 and 2005 have shown that the virus has mutated and variants of H5N1 strains have emerged. Information on the number of confirmed clinical cases due to H5N1 strains can be located at the World Health Organization's website.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 disturbing events have highlighted the need for influenza vaccines against potential pandemic strains.

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

Licensure of pandemic influenza vaccines may be sought either as a supplement to an existing Biologics License Application (BLA) or as a new BLA using the accelerated approval regulations (21 CFR Part 601 Subpart E). This section provides recommendations for clinical data that would support such approvals for pandemic influenza vaccines. CBER has also prepared similar draft guidance for trivalent influenza inactivated vaccines. For an opportunity to comment on that guidance, please refer to CBER's draft guidance document, "Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines" dated March 2006.

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 of the PHS Act, 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

² See www.who.int/csr/disease/avian_influenza/country/en/index.html.

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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 as a Supplement to a U.S. Licensed Trivalent Inactivated Influenza Vaccine

As discussed above, clinical trials would be needed to support the appropriate dose and regimen of the pandemic influenza vaccine. These trials should include an assessment of immunogenicity and safety. Data from these trials should be submitted as a clinical supplement to the existing BLA. Once a pandemic influenza vaccine against a new influenza subtype has been licensed, further clinical data with a variant of that subtype would likely not be needed for licensure. Information to support a change in the viral subtype variant included in the vaccine should be submitted as a manufacturing supplement to the existing 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 percent of subjects achieving an HI antibody titer $\geq 1:40$, and 2) rates of seroconversion, defined as a four-fold rise in HI antibody titer post-vaccination. The geometric mean titer (GMT) should be included in the results. These data and the 95% confidence intervals (CI) of the point estimates of these evaluations should be provided with the BLA clinical supplement.

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, 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. Other immunologic assays, such as the microneutralization assay, might also be used to support the approval of a pandemic influenza vaccine as a clinical supplement to the BLA (Ref. 18).

2. Safety

Local and systemic reactogenicity events 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 should be monitored and collected for all subjects throughout the duration of the studies. The protocol should include a clinic visit or telephone contact at least six months post-vaccination to ascertain additional serious adverse events and

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new onset of chronic illnesses that may have occurred in the interim. Safety data gathered from the six month post-vaccination evaluation should be submitted when available. This may occur after submission or approval of the supplement.

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 manufacturer's vaccine to support approval for use in the pediatric population should depend on available clinical data for that trivalent influenza vaccine. The timing of the clinical development in the pediatric population warrants discussion with CBER. All sponsors have obligations to study pediatric populations as outlined in the Pediatric Research Equity Act of 2003.

B. Approval of a Pandemic Influenza Vaccine as a Supplement to a U.S. Licensed Trivalent Live Attenuated Influenza Vaccine

As for pandemic influenza vaccines discussed in section III.A. above, clinical trials to support the appropriate dose and regimen of a live attenuated pandemic influenza vaccine would be needed and should include an assessment of immunogenicity and safety. These data should be submitted as a clinical supplement to the existing BLA for the trivalent live attenuated influenza vaccine. However, because of the theoretical concern for reassortment between a live attenuated pandemic influenza vaccine strain with other circulating influenza strains, it is anticipated that a licensed live attenuated influenza vaccine would be labeled for use only after the onset of a pandemic influenza outbreak.

1. Immunogenicity

Data to support the selected dose and regimen should be based on the evaluation of immune responses elicited by the vaccine. The HI antibody response may be appropriate for the evaluation of the new pandemic influenza vaccine strain. For the HI antibody assay, we recommend the following endpoints: 1) the percent of subjects achieving an HI antibody titer $\geq 1:40$, and 2) rates of seroconversion, defined as a four-fold rise in HI antibody titer post-vaccination. The GMT should be included in the results. These data and the 95% CI of the point estimates of these evaluations should be provided with the BLA clinical supplement. Given the route of administration of live attenuated influenza vaccines, other assays especially those that assess mucosal immunity may also be appropriate if they are validated and are shown to be predictive of effectiveness.

2. Safety

Clinical studies with live attenuated influenza pandemic vaccines performed in advance of a pandemic influenza outbreak present special considerations. 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

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should be well characterized from all subjects. Contact precautions should be in place for study subjects and study personnel for the duration of the study. 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 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 should be monitored and collected for all subjects throughout the duration of the studies. 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 may be submitted post-approval.

C. Accelerated Approval of a BLA for a Pandemic Influenza Vaccine (i.e., Not as a BLA Supplement to an Existing U.S. Licensed Influenza Vaccine)

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 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). Post-marketing 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 products approved under these regulations may be withdrawn, for example, if the clinical study fails to verify the clinical benefit or the sponsor fails to perform the required post-marketing study with due diligence (21 CFR 601.43(a)(2)).

For pandemic influenza vaccines, evaluation of an 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

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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 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 vaccines are limited. Accelerated approval of new live attenuated 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 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 post-marketing studies. 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.

- 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) percent of subjects achieving an HI antibody titer \geq 1:40.

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

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trivalent inactivated vaccines.³ 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 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.
- The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer $\geq 1:40$ should meet or exceed 70%.

For adults ≥ 65 years of age:

- The lower bound of the 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer $\geq 1:40$ 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 ($\text{GMT}_{\text{U.S. licensed vaccine}}/\text{GMT}_{\text{new vaccine}}$) 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%.

³ CBER has prepared similar draft guidance for trivalent influenza vaccines. For an opportunity to comment on that guidance, please refer to CBER's draft guidance, "Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines" dated March 2006.

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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 should be collected from subjects enrolled in pre-licensure clinical trials intended to support the accelerated approval of a pandemic vaccine. The monitoring of these subjects should follow the outline described in section III.A.2. above. In addition, safety laboratory tests, to include hematologic and clinical chemistry evaluations, should be obtained pre- and post-vaccination in the first clinical study(ies). A total safety database large enough to rule out a serious adverse event that occurs at a rate of 1 in 300 may be adequate. The size of the pre-licensure safety database warrants discussion with CBER, especially for vaccines manufactured using novel processes and for adjuvanted pandemic vaccines. This determination would be influenced by factors such as the nature of the new manufacturing process and available clinical data. Safety data to support use in pediatric populations would also be needed and should be submitted as part of the BLA or as a supplement if the indication is sought at a later time.

3. Post-marketing Confirmatory Studies

a. Confirmatory studies if a sponsor pursues U.S. licensure of an annual TIV vaccine

Sponsors seeking approval of a pandemic influenza vaccine strain are encouraged to pursue development of a trivalent inactivated influenza vaccine using the same manufacturing process as used for the pandemic influenza vaccine (see footnote 3). Approval of the trivalent inactivated vaccine, other than through accelerated approval, may help fulfill the post-marketing requirement to verify the clinical benefit of the pandemic influenza vaccine.

b. Confirmatory studies if a sponsor does not pursue U.S. licensure of annual trivalent inactivated influenza vaccine

The sponsor would need to conduct one or more post-marketing field effectiveness studies to verify the clinical benefit of the vaccine. The sponsor should discuss its plans with CBER and include its plan or approach to conduct a study with its BLA application.

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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 “split virus” and whole virus inactivated pandemic influenza vaccines propagated in embryonated chicken eggs. The recommendations also apply to licensure of cell culture derived, recombinant hemagglutinin-based and adjuvanted pandemic influenza vaccines. Detailed information on product characteristics and manufacturing processes are needed for all new vaccines, regardless of their derivation (see footnote 1). Accelerated approval would not apply to a live attenuated pandemic influenza vaccine until a surrogate endpoint that is reasonably likely to predict clinical benefit is identified.

2. Clinical Lot Consistency

The objective of a clinical lot consistency study is the demonstration that three consecutively manufactured final 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 not exceed 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. CBER may decide, on a case by case basis, that lot consistency may be evaluated and incorporated in the post-marketing commitment studies. This determination would be influenced by factors such as the manufacturing process used for the pandemic influenza vaccine and available clinical experience.

3. Adjuvanted Pandemic Vaccines

Small studies of inactivated pandemic influenza vaccines have shown that more antigen per dose and more than one dose are needed to elicit immune responses comparable to those elicited following a single dose of an annual trivalent inactivated influenza vaccine (Ref. 23). Use of an adjuvant might reduce the amount of antigen needed to elicit immune responses to protect against influenza illness. All influenza vaccine products formulated with an adjuvant should be submitted as new products. Data supporting their approval should be submitted to a new BLA.

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- Dose and Formulation Selection

At an early stage of development, the sponsor should demonstrate the added value of the adjuvant given with the antigen. Assuming that the vaccine is a hemagglutinin-based product, the HI antibody assay may be appropriate to evaluate the immune response.

A comparative study of adjuvanted vs. non-adjuvanted vaccines should demonstrate that the immune response elicited by the adjuvanted antigen is significantly better than that elicited by the same antigen alone. Differences in HI antibody titer and seroconversion should be meaningful (i.e., significant by assessment of p-value). For study sample size determination, the sponsor should pre-define what would constitute a meaningful difference. As an example, CBER may view a 0.3 \log_{10} mean difference (same as a two-fold difference in GMT ratio) for the HI antibody titers and a 15% difference in seroconversion rates as meaningful differences. The sponsor should also justify values assumed for the standard deviation of the \log_{10} HI antibody titers. The HI antibody titers will typically require log transformation (i.e., HI antibody titers converted to \log_{10} HI antibody titers) in order to produce data that may satisfy the normality assumption of certain parametric statistical tests. A t-test (or Wilcoxon rank-sum test if the normality assumption does not hold) may be used to compare the mean \log_{10} HI antibody titers, and the Fisher's exact test may be used to compare the seroconversion rates. Both tests should be one-sided at the 2.5% significance level. The study should be adequately powered to meet both analysis endpoints. Alternative analyses, or ones allowing pre-specified covariate adjustment, may be acceptable and should be discussed in advance 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., intradermal or transdermal vaccination, which may involve the use of novel devices) are being investigated with the goal of reducing the amount of antigen needed to elicit immune responses that are likely to protect against influenza illness. Such strategies might then allow the expansion of the available vaccine supply. In cases where no novel manufacturing concerns are raised (such as intradermal administration of a vaccine formulation licensed for subcutaneous administration), approval may be possible as a clinical 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.

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5. Post-marketing Studies

a. Effectiveness

As discussed in section III.A. above, pandemic influenza vaccines may be approved on the basis of immunogenicity data submitted as a clinical supplement to an existing BLA for a trivalent influenza vaccine. Sponsors are encouraged to develop plans to monitor the effectiveness of their pandemic influenza vaccine in the event of a pandemic outbreak. As discussed in section III.C. above, for pandemic influenza vaccines approved under an accelerated approval, sponsors will need to conduct a post-marketing effectiveness study to verify clinical benefit, and should include their study plans with their application.

b. Safety

Sponsors are encouraged to develop a plan to monitor the safety of their vaccine in the event of a pandemic influenza outbreak. Furthermore, sponsors may wish to enhance the safety database of their pandemic influenza vaccine by conducting safety studies prior to a pandemic influenza outbreak, for example among individuals identified by public health authorities for pre-pandemic vaccination. The safety monitoring for such studies should follow the outline described in section III.A.2. above. Whereas all subjects would be monitored for serious adverse events, detailed local and systemic reactogenicity events to further quantify common events might be collected from a representative subset. We recommend that vaccines manufactured with novel processes and adjuvants be evaluated more extensively. In addition, FDA and the Centers for Disease Control and Prevention plan to conduct enhanced safety surveillance during early use of the vaccine.

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