Guidance for Industry

Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

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

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This document is intended to provide to you, sponsors of seasonal inactivated influenza vaccines, guidance on clinical development approaches to support a Biologics License Application (BLA). The approaches in this guidance apply to both nonadjuvanted and adjuvanted hemagglutinin-based seasonal 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. This document does not address live attenuated influenza vaccines or influenza vaccines that do not rely on immunity to a hemagglutinin component.

We, FDA, recognize that in the past there have been monovalent and bivalent inactivated influenza vaccines for seasonal influenza. To provide flexibility for evolving public health needs, including the development of vaccines with either more than three or fewer than three antigens, this guidance uses the term "seasonal inactivated influenza vaccine."

This document does not address the nonclinical or early clinical development of investigational vaccines. Successful evaluations of nonclinical and early clinical development are important steps before proceeding with additional 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.

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

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.

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 inactivated trivalent vaccines are formulated to prevent influenza illness caused by these influenza viruses. Because of the frequent emergence of new influenza variant strains, the antigenic composition of influenza vaccines needs to be evaluated yearly, and the trivalent inactivated influenza vaccines are reformulated almost every year. The immune response elicited by previous vaccination may not be protective against new variants.

The Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) has expanded the recommendations for receipt of influenza vaccination to include an increasing scope of at risk populations, currently including pregnant women, persons 50 years of age and older, and children 6 to 59 months of age (Refs. 7, 8, and 9). Increased demand for influenza vaccines, including that resulting from the broader recommendations, the withdrawal from the U.S. market by several influenza vaccine manufacturers, and intermittent decreases in vaccine production due to manufacturing problems have led to shortages or delays in the availability of influenza vaccine over the past several seasons. These shortages highlight both the complexity of the production process and the need to increase the availability of influenza vaccines from multiple manufacturers. Currently, even with full production, manufacturing capacity would not produce enough seasonal influenza vaccine to vaccinate all those for whom the vaccine is now recommended. Finally, the availability of adequate supplies of licensed seasonal inactivated influenza vaccines from multiple manufacturers will be of value in responding to the emergence of a new pandemic influenza strain.

III. CLINICAL DATA TO SUPPORT THE LICENSURE OF SEASONAL INACTIVATED INFLUENZA VACCINES

Licensure of seasonal inactivated influenza vaccines may be sought through the submission of an application by means of either a traditional or accelerated pathway. This Section provides recommendations for clinical data to support traditional and accelerated license approvals for new seasonal inactivated influenza vaccines. CBER has prepared similar guidance for pandemic influenza vaccines, "Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines." [2]

A. Traditional Approval of a BLA for a New Seasonal Inactivated Influenza Vaccine

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))." [3]

1. Effectiveness

   As discussed above, demonstration of effectiveness against influenza illness in an adequate and well-controlled clinical study would support licensure of a new seasonal inactivated influenza vaccine. In this document, a clinical endpoint efficacy study refers to a clinical trial in which influenza illness is assessed as the primary endpoint. The study design should take into account the following parameters:

   a. The study population should be carefully considered. A placebo-controlled clinical efficacy study conducted in a population that is not at increased risk for complications from influenza would allow for a precise estimation of clinical effectiveness against influenza illness (absolute efficacy). The ACIP usually lists, at least annually, those persons who are considered to be at increased risk for influenza complications; we will rely on that list (Ref. 10).

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

Alternatively, a population at increased risk for influenza illness complications may be studied, but an adequate sample size should be used to demonstrate non-inferiority of the new vaccine to a U.S. licensed product with regard to clinical effectiveness.

b. The case definition for influenza illness should be prospectively defined. Inclusion of culture confirmation, viral typing and antigenic characterization in the case definition increases the specificity. The increased specificity allows for a more precise estimate of vaccine effectiveness and would likely reduce the sample size needed to assess effectiveness. Additionally, culture confirmation would facilitate interpretation of study results in the event that circulating influenza strains do not match antigen components contained within the vaccine. An analysis of whether the immune response elicited by the vaccine correlates with protection against influenza illness will depend upon the use of a specific case definition (e.g., culture confirmation of influenza).

c. Study sample size calculations should be based on estimates of vaccine effectiveness and influenza attack rates. The study should be powered to assess the lower bound of the two-sided 95% confidence interval (CI) of vaccine effectiveness, anticipated to be substantially above zero (e.g., in the range of 40 to 45%).

d. Immunogenicity evaluations in a substantial number of study participants are important elements of the study design. Characterization of the immune response elicited post-vaccination in the clinical endpoint efficacy study may allow for extrapolating the effectiveness to other populations if they have an immune response to vaccination comparable to that observed in the clinical endpoint efficacy study. Furthermore, immune response data collected in the course of a prospectively designed clinical endpoint efficacy study may lead to the establishment of an immune correlate of protection. Such a correlate could greatly facilitate future influenza vaccine development.

2. Additional Studies to Support the Effectiveness of the Vaccine in Populations Not Included in the Clinical Efficacy Study

Some populations who are at increased risk for complications from influenza vaccination (e.g., individuals 6 to 59 months of age and those 65 years of age and older) may not have been included in the clinical endpoint efficacy study because of the challenges in conducting a comparative efficacy study. Effectiveness studies in these populations can be based on appropriate immunogenicity endpoints.

a. Immunogenicity bridging studies can be conducted to compare the immune response observed in the clinical endpoint efficacy study to that elicited in other populations. Appropriate endpoints may be the hemagglutination

inhibition (HI) antibody responses to each viral strain included in the vaccine. Studies should be adequately powered to assess the following co-primary endpoints for each of these viral strains: 1) geometric mean titer (GMT), 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 ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer. (See recommendations for these endpoints outlined in Section III.B.1.a.). Point estimates and the two-sided 95% CI of these evaluations should be provided in the BLA. While this approach may expand the use of the new vaccine in additional populations, an important consideration is that immune responses in the very young and the elderly might be lower than those observed in healthy adults enrolled in a placebo-controlled clinical endpoint efficacy study. Additionally, changes to the annual formulation of the vaccine might complicate the design of such studies. Identification of an immune correlate of protection during the course of a clinical endpoint efficacy study may facilitate the design and interpretation of such bridging studies.

b. Alternatively, non-inferiority immunogenicity studies comparing a new vaccine to a U.S. licensed seasonal vaccine may support the use of the new vaccine in populations not included in the clinical endpoint efficacy study. This is true when the comparator vaccine is indicated for use in the population under study and when the comparator vaccine has clinical effectiveness data (i.e., not a U.S. licensed seasonal inactivated vaccine granted accelerated approval with its clinical benefit awaiting confirmation). Studies should be adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: 1) GMT, and 2) seroconversion rates (as outlined in Section III.B.1.a.).

3. Safety

The safety of the new vaccine should be well characterized in pre-licensure clinical trials. 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.[4] 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.

[4] For further information, see the FDA "Draft Guidance for Industry: Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" available at http://www.fda.gov/cber/vaccine/vacpubs.htm. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

For vaccines using novel manufacturing processes and/or adjuvants, laboratory safety tests including hematologic and clinical chemistry evaluations, may be needed pre-and post-vaccination in the first clinical studies. Depending on those findings and pre-clinical data, additional clinical laboratory tests in later studies may be needed.

The total size of the safety database should depend, in part, on the range of the age indication being sought, signals raised during pre-clinical studies and early clinical studies, and the amount of clinical experience associated with the particular manufacturing process and the adjuvant, if one is included in the influenza vaccine. 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. We recommend that you assess the safety of your investigational vaccine in several thousand subjects who receive the product in the controlled clinical trials described above. You are encouraged to initiate an early dialogue with CBER to agree on the size of the safety database needed to support product licensure.

4. Pediatrics

   The timing of the clinical development and the size of the safety database to support use in the pediatric age groups warrants discussion with CBER. Please refer to Section III.C. – Additional Considerations, paragraph 4, for a discussion of the Pediatric Research Equity Act (PREA).

B. Accelerated Approval of a BLA for a New Seasonal Inactivated Influenza Vaccine

Accelerated approval may be granted for certain biological products 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. (See Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (21 CFR Part 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)).

The option to pursue an accelerated approval pathway for seasonal inactivated influenza vaccines is also available to sponsors if a shortage of influenza vaccine exists for the U.S. market at the time the new vaccine is approved. We interpret the accelerated approval regulation, 21 CFR 601.40, as allowing accelerated approval of an influenza vaccine during a shortage because influenza is a serious and sometimes life-threatening illness. Providing prophylaxis to those who would not otherwise be immunized during a shortage does certainly provide a meaningful benefit over the then-existing treatments, which are in short supply at that time. We understand a shortage to exist when the supply of influenza vaccine is inadequate to immunize all persons for whom the CDC recommends annual vaccination. The CDC estimates that there are 185 million individuals in the United States for whom influenza vaccination is recommended annually (Ref. 11).

For 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 the viral surface, are important for cell-receptor binding. The immune response to the hemagglutinin as measured by the presence of serum HI antibodies is an important protective component following vaccination and/or infection. However, 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.

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. 12 and 13). Seroconversion and GMT have been used as measures of vaccine activity (Refs. 14 and 15).

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

To be considered for accelerated approval, a BLA for a new seasonal inactivated influenza vaccine should include results from one or more well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory postmarketing studies of clinical effectiveness in preventing influenza during the next influenza season. 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. We are open to considering other study designs, and 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 non-inferiority immunogenicity trial of HI antibody responses to the new vaccine as compared to a U.S. licensed seasonal inactivated influenza vaccine (except for those granted accelerated approval whose clinical benefit awaits confirmation) may support an accelerated approval. The study should be adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine (e.g., a total of six co-primary endpoints for a trivalent vaccine): 1) GMT, and 2) seroconversion rates. Recommendations for the co-primary endpoints include the following:

      - The upper bound of the two-sided 95% CI on the ratio of the GMTs ($GMT_{U.S.\ licensed\ vaccine}/GMT_{new\ vaccine}$) 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 ($Seroconversion_{U.S.\ licensed\ vaccine} - Seroconversion_{new\ vaccine}$) should not exceed 10 percentage points.

   b. Alternatively, 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 is adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: 1) seroconversion rates, and 2) percentage of subjects achieving an HI antibody titer $\geq$ 1:40. A saline placebo may be an acceptable control if the population studied is not a group for whom seasonal influenza vaccination is routinely recommended by the ACIP due to increased risk of complications from influenza illness or if the study is conducted off-season. If a study is conducted just prior to the influenza season in populations who are at increased risk from influenza illness, use of a U.S. licensed influenza vaccine as a control may be appropriate. The purpose of the control arm in this type of study design, whether it is a saline-placebo or a U.S. licensed influenza vaccine, is primarily to provide a comparative assessment of safety and to provide a general assurance of immunogenicity response from the new vaccine.

For example, the following recommendations, which have been modified from guidelines by the currently-titled, "Committee for Medicinal Products for Human Use of the European Medicines Agency" (Ref. 14), may support an accelerated approval.

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%.

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 new seasonal inactivated influenza vaccine (21 CFR 312.23, 312.32, 312.56, 312.60 and 312.62). The monitoring of these subjects should follow the outline for safety evaluations described in Section III.A.3. above. 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 clinical trials, using the Clopper-Pearson method. However, the size of the pre-licensure safety database, especially for seasonal influenza vaccines manufactured using novel processes such as cell-culture and for seasonal influenza vaccines that contain novel adjuvants, would be influenced by factors such as the nature of the new manufacturing process and available pre-clinical 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, 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 (see Section III.C.4. – Pediatric Research Equity Act).

3. Postmarketing Confirmatory Studies

For the design of postmarketing studies the sponsor should refer to studies described in Section III.A.1. on effectiveness data to support traditional approval of new seasonal inactivated influenza vaccines.

C. Additional Considerations

1. Types of Influenza Vaccines

U.S. licensed seasonal inactivated influenza vaccines include those that are propagated in embryonated chicken eggs, and the virus is disrupted in the manufacturing process yielding "split virus" inactivated vaccines. The current recommendations regarding clinical effectiveness and safety data to support licensure apply to both nonadjuvanted and adjuvanted hemagglutinin-based seasonal vaccines, including "split virus," subunit, and whole virus inactivated vaccines propagated in embryonated chicken eggs or cell-culture, and to recombinant hemagglutinin-based protein, and DNA vaccines that express hemagglutinin. Of note, vaccines manufactured by processes different from those used for currently licensed vaccines in the United States will likely require different pre-clinical evaluations. 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 each 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 to each of the viral strains 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 new influenza vaccine and available manufacturing and clinical experience.

3. Adjuvanted Seasonal Inactivated Influenza Vaccines

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 influenza viral strains. However, vaccine formulations containing adjuvants may pose additional safety risks.

Data supporting the safety of the adjuvanted formulation and 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 with 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 will 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 a difference parameter) may be sufficient to demonstrate the added value of the adjuvant.

  In the setting of a shortage for seasonal influenza vaccines, defined in Section II, use of an adjuvant may be supported by data from a comparative study demonstrating non-inferiority immune responses

elicited by the adjuvanted vaccine containing a lower amount of antigen than the dose-optimized non-adjuvanted vaccine formulation. Other approaches may be possible, and we encourage you to discuss your proposal(s) with us.

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

- Adding an Adjuvant to a Licensed Seasonal Influenza Vaccine

  If an adjuvant is added to a licensed seasonal influenza vaccine for use without antigen sparing effects (i.e., the dose of the antigen is not changed), the immune response elicited by the adjuvanted vaccine formulation should be substantially better than that elicited by the unadjuvanted vaccine for the study population. A comparative clinical trial may first be done under accelerated approval using immunogenicity endpoints, followed by a confirmatory postmarketing study of comparative effectiveness in that study population. For accelerated approval, meaningful differences in HI antibody titer and seroconversion rates between adjuvanted and unadjuvanted formulations should be specified and justified. Meaningful differences may also include a demonstration of cross-reactivity against drifted strains. For confirmatory postmarketing studies, meaningful differences in clinical endpoints should be specified and justified.

4. Pediatric Research Equity Act

   The Pediatric Research Equity Act of 2003 (PREA) (Public Law 108-155) (section 505B of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355c) 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 clinical efficacy 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. 16). As stated in that document, FDA encourages the submission of pediatric development plans to FDA as early as possible in the vaccine development process.

5. Postmarketing Evaluations

   As part of your BLA submission, you should include a pharmacovigilance plan, especially if the vaccine involves novel manufacturing processes and/or novel adjuvants. The format of these submissions should be in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E2E guidance) (Ref. 17).

   In addition, routine pharmacovigilance should include submission of adverse event reports to the Vaccine Adverse Event Reporting System in accordance with 21 CFR Part 600, Subpart D. You may be requested to consider expedited reporting of some adverse event reports (e.g., serious labeled adverse events) and dose distribution data for the vaccine.

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