Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or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 Antonia Geber, M.D., or Donna Chandler, Ph.D., at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2006

Table of Contents

I. INTRODUCTION **1**

II. BACKGROUND **2**

III. CLINICAL DATA TO SUPPORT THE LICENSURE OF TRIVALENT INACTIVATED INFLUENZA VACCINES **3**

A. Traditional Approval of a BLA for a New Trivalent Inactivated Influenza Vaccine **3**

1. Effectiveness 3
2. Additional Studies to Support the Effectiveness of the Vaccine in Populations Not Included in the Clinical Efficacy Study 4
3. Safety 5

B. Accelerated Approval of a BLA for a New Trivalent Inactivated Influenza Vaccine **6**

1. Effectiveness 7
2. Safety 9
3. Post-marketing Confirmatory Studies 9

C. Additional Considerations **9**

1. Types of Influenza Vaccines 9
2. Clinical Lot Consistency 9
3. Adjuvanted Trivalent Inactivated Influenza Vaccines 10

IV. REFERENCES **11**

Guidance for Industry

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 trivalent inactivated influenza vaccines, guidance on clinical development approaches to support a Biologics License Application (BLA). Currently two classes of trivalent vaccines are licensed in the United States, "split virus" inactivated trivalent vaccines and a live attenuated trivalent vaccine. In this document we, FDA, summarize clinical development approaches to facilitate and expedite the licensure of new "split virus" trivalent inactivated influenza vaccines, and we address both traditional and accelerated approval. These approaches are also applicable to vaccines made with other manufacturing processes; e.g., whole virus inactivated, cell-culture derived inactivated, recombinant hemagglutinin-based protein, and adjuvanted influenza vaccines. This document does not address live attenuated influenza vaccines or influenza vaccines that do not contain a hemagglutinin component.

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" dated January 1999[1] (64 Federal Register 518, January 5, 1999). 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/gdlns/cmcvacc.pdf.

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, 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 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 no longer be protective against new variants. Annual vaccination is indicated for persons who wish to be protected from influenza illness and is recommended for people who are at high risk for complications of influenza illness (Ref. 7).

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 additional at risk populations, such as pregnant women, persons 50 years of age and older, and children 6 to 23 months of age (Refs. 8, 9, and 10). The increased demand for influenza vaccines resulting from the broader recommendations, coupled with the withdrawal from the U.S. market by several influenza vaccine manufacturers over the same time period and the recurrent instances where some manufacturers were unable to provide influenza vaccines to the market due to manufacturing problems, has led to shortages or delays in the availability of influenza vaccine over the past several seasons. These shortages highlighted the need for increased availability of influenza vaccines from multiple manufacturers. In addition the

availability of adequate supplies of licensed trivalent 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 TRIVALENT INACTIVATED INFLUENZA VACCINES

Licensure of trivalent inactivated influenza vaccine may be sought through either traditional or accelerated pathways. This section provides recommendations for clinical data to support traditional and accelerated license approvals for new trivalent inactivated influenza vaccines. CBER has prepared similar draft guidance for pandemic influenza vaccines. For an opportunity to comment, please refer to CBER's draft guidance, "Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" dated March 2006.

A. Traditional Approval of a BLA for a New Trivalent 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 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 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))."

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 trivalent 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 at increased risk for influenza complications; we will rely on that list (Ref. 11). 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 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 23 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 of the three viral strains contained within the vaccine.

Studies should be adequately powered to assess the following co-primary endpoints: 1) geometric mean titer (GMT), and 2) rates of seroconversion, defined as a four-fold rise in antibody titer post-vaccination. (See recommendations for these six endpoints outlined in section III.B.1.a.). 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 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 vaccine may support the use of the new vaccine in populations not included in the clinical endpoint efficacy study. 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. 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.

The total size of the safety database should depend, in part, on the range of the age indication being sought. 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. It is recommended that several thousand subjects receive the investigational vaccine in the controlled clinical trials described above, and assessment of safety will be available from these study participants.

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. 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. All sponsors have obligations to study pediatric populations as outlined in the Pediatric Research Equity Act of 2003.

B. Accelerated Approval of a BLA for a New Trivalent 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 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)).

The option to pursue an accelerated approval pathway for trivalent inactivated influenza vaccines is 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. 12).

For 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 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, 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. 13 and 14). Seroconversion and GMT have been used as measures of vaccine activity (Refs. 15 and 16).

For the purposes of accelerated approval of trivalent 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 trivalent inactivated influenza vaccine should include results from one or more well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory post-marketing studies 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.

a. A non-inferiority immunogenicity trial of HI antibody responses to the new vaccine as compared to a U.S. licensed trivalent inactivated influenza vaccine 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 (i.e., a total of six co-primary endpoints): 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 ($GMT_{\text{U.S. licensed vaccine}}/GMT_{\text{new vaccine}}$) 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 ($Seroconversion_{\text{U.S. licensed vaccine}} - Seroconversion_{\text{new vaccine}}$) should not exceed 10%.

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 was adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: 1) seroconversion rates, and 2) percent of subjects achieving an HI antibody titer ≥ 1:40. A saline placebo may be an acceptable control if the population studied is not at 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, not effectiveness.

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. 15), may support an accelerated approval.

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 ≥ 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 ≥ 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 should be collected from subjects enrolled in pre-licensure clinical trials intended to support the accelerated approval of a new trivalent inactivated influenza vaccine. The monitoring of these subjects should follow the outline for safety evaluations described above for traditional approval. 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 vaccines. This determination may 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 will also be needed and should be submitted as part of the BLA or as a supplement if use in a pediatric population is sought at a later time (see Pediatric Research Equity Act of 2003).

3. Post-marketing Confirmatory Studies

For the design of post-marketing studies the sponsor should refer to studies described in section III.A.1. on effectiveness data to support traditional approval of new trivalent inactivated influenza vaccines.

C. Additional Considerations

1. Types of Influenza Vaccines

Currently, all three U.S. licensed trivalent inactivated influenza vaccines 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 new split virus trivalent inactivated influenza vaccines propagated in embryonated chicken eggs. However, they also apply to licensure of new whole virus inactivated, cell culture derived inactivated, recombinant derived hemagglutinin-based and adjuvanted influenza vaccines. 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 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 each 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 three 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. 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 new influenza vaccine and available clinical experience.

3. Adjuvanted Trivalent Inactivated Influenza Vaccines

Use of an adjuvant might reduce the amount of antigen needed to elicit immune responses to protect against influenza illness and might enhance vaccine supply. 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.

- 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 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.

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(RR08):1-40.

8. 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. 1997;46(RR-9):1-25.

9. 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. 2000;49(RR-3):1-38.

10. 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. 2004;53(RR-6):1-40.

11. Centers for Disease Control and Prevention. Update: Influenza Vaccine Supply and Recommendations for Prioritization During the 2005--06 Influenza Season. MMWR Morbidity and Mortality Weekly Report. 2005;54(34);850:1-3.

12. Testimony of Julie L. Gerberding, M.D., M.P.H., Director, Centers for Disease Control and Prevention, on "Protecting the Public's Health: CDC Influenza Preparedness Efforts" before The Committee on Government Reform, U.S. House of Representatives, 2/12/2004. (Available at: http://www.cdc.gov/washington/testimony/In2122004200.htm).

13. 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.

14. 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.

15. 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.

16. 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.