Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review

Regulatory Considerations Regarding the Use of Novel Influenza A (H1N1) Virus Vaccines

Vaccines and Related Biological Products Advisory Committee
July 23, 2009

1.0 Introduction:

1.1 General: This briefing document reflects the current understanding of the novel influenza A (H1N1) virus pandemic and the current expectations of vaccine availability and clinical data required to license or permit emergency use of a monovalent vaccine. However, as the situation evolves regulatory approaches and considerations may change, depending on surveillance and epidemiology data and decisions by the U.S. government and public health policy makers. Data and regulatory considerations presented in this document reflect the status as of June 26, 2009, thus, the contents should be reviewed in that context.

1.2 Novel influenza A (H1N1) disease: On April 21, 2009 CDC reported that two cases of febrile respiratory illness were caused by infection with swine influenza A (H1N1) virus (*MMWR, 2009, 58(15): 400-402*). This influenza strain was genetically similar to viruses isolated from patients in Mexico (*MMWR 2009; 58(17):463-466*). On April 26, 2009 the Secretary of the Department of Health and Human Services determined that a public health emergency involving swine influenza A exists. On June 11, 2009 WHO raised the level of pandemic alert from phase 5 to phase 6, indicating that human-to-human spread of the virus had occurred in at least two countries in one WHO region and sustained community level outbreaks in at least one other country in another region. As of June 26, 2009 a total of 59,814 cases including 263 deaths were reported worldwide. The US had reported 21,449 cases including 87 deaths (http://www.who.int/csr/don/2009_06_26/en/index.html). To date the majority of cases in all countries have occurred among adolescents and young adults (*Wkly Epi Rec 2009; 84:249-260*). A recent report (*MMWR 2009; 58(21):585-589*) noted that in Mexico, among over 5000 laboratory confirmed cases of novel influenza A (H1N1) infection, ~42% of patients were <15 years, ~32% were aged 15-29 years, ~24% were aged 30-59 years, and ~2% were aged ≥ 60 years. Within the U.S. the age distribution of confirmed cases has been similar (*MMWR 2009 58(17): 453-458*).

A summary of clinical features of human infection with the novel influenza A (H1N1) has been published by the WHO (*Wkly Epi Rec 2009; 84:185-189*). This report notes that most cases were uncomplicated, typical influenza-like illness and

patients recovered spontaneously. Within the U.S. approximately 5-9% of confirmed cases have been hospitalized (*MMWR 2009; 58(17): 453-458* and *MMWR 2009; 58(19): 536-541*). In Mexico approximately 6% of confirmed cases have been hospitalized. Approximately half of patients hospitalized in the U.S. and 21 of 45 (46%) fatal cases in Mexico, for whom data are available, have had co-morbidities such as diabetes, obesity and cardiovascular disease or were pregnant. In Mexico among 45 fatal cases, 54% were among previously healthy people most of whom were 20-59 years of age. In the U.S., among 13 pregnant women with influenza illness due to the novel influenza A (H1N1) and for whom data are available 3 were hospitalized, one of whom died (*MMWR 2009; 58(18)497-500*).

1.3 Cross reactive antibodies to novel influenza A (H1N1): CDC recently reported the level of cross reactive antibody to the novel influenza A (H1N1) virus in stored pre- and post-vaccination sera from 359 U.S. children and adults vaccinated with seasonal influenza vaccines from 2005 to 2009 (*MMWR 2009; 58:521-524*). Among 60 adults >60 years of age, 33% had pre-vaccination antibodies that reacted to the novel influenza A (H1N1) virus, as compared to 6%-9% of the pre-vaccination samples from those aged 18-64 years. Adults vaccinated with seasonal inactivated influenza vaccine had a small increase in antibodies against the novel influenza A (H1N1) virus. Among 79 children 6 months to 9 years of age, there was little evidence of pre- or post-vaccination antibody cross reactive to the novel influenza A (H1N1). These data suggest that while older persons may have some level of preexisting immunity to the novel H1N1 strain, children and younger adults have no or low levels of serum antibody, respectively, that are cross reactive to the novel influenza A (H1N1) virus.

Based on these data as well as historical data with A/New Jersey(NJ)/76 (*Boyer et al. JID 1977; 136:S579-S583*) and data accrued with H5N1 vaccine (*Treanor et al. NEJM 2006; 354:1343-135*1) a single dose of monovalent novel influenza A (H1N1) vaccine may not provide an adequately protective immune response.

2.0 H1N1 Vaccine

2.1 Strain Selection: The WHO publication "Characteristics of the emergent influenza A (H1N1) viruses and recommendations for vaccine development," recommended that novel influenza A (H1N1) vaccines should contain A/California/7/2009 (H1N1)v-like virus (http://www.who.int/csr/resources/publications/swineflu/vaccine_recommendations/en/). To date (June 26, 2009, http://www.cdc.gov/flu/weekly/) CDC has antigenically characterized 144 novel A (H1N1) viruses. All are related to the A/California/07/2009 (H1N1) reference virus selected by WHO as a potential candidate for novel influenza A (H1N1) vaccine. As of June 15,2009 two classical (X-179A and IVR-153) and three reverse genetics (A/Texas/05/2009(H1N1)-PR8-IDCDC-RG15; H1N1/A/California/07/2009

NIBRG121; (H1N1)v-PR8-CBER-RG2) reassortants that have undergone virus characterization and are suitable for vaccine production, were sent to all the WHO collaborating centers and vaccine manufacturers to prepare seed virus for vaccine production.

Ferret safety testing for X-179A and RG15 are available but tests on other candidate vaccine viruses are still in progress. Initial growth studies have suggested that the virus yield from A/California/7/2009 (H1N1)v reassortants are lower relative to the yields of many reassortants used for seasonal influenza vaccines, but additional studies to assess virus yields are underway. Status of candidate vaccine virus development can be found on the WHO Epidemic and Pandemic Alert & Response Homepage website http://www.who.int/csr/en/.

2.2 Vaccine Manufacturers: All manufacturers of US-licensed seasonal influenza virus vaccines are prepared to make monovalent novel influenza A (H1N1) virus vaccine available for the US market. To date the U.S. Dept. of Health and Human Services (DHHS) expects the following manufacturers to supply inactivated influenza vaccine for the US market: Novartis Vaccines and Diagnostics, Ltd., sanofi pasteur, Inc., CSL Ltd. and GlaxoSmithKline Biologicals. MedImmune will supply live attenuated novel influenza A (H1N1) virus vaccine.

2.3 Manufacturing Considerations: As of mid-June, 2009 the timeline for novel influenza A (H1N1) vaccine manufacture is uncertain. Some manufacturers have targeted mid-late June to begin their first production of vaccine, but the timing will be dependent upon development of seed viruses with acceptable growth characteristics. For inactivated vaccines, potency reagents will be needed for formulation of vaccine for clinical trials. WHO is working with all of WHO Essential Reference Laboratories (ERL), including CBER, to prepare potency testing reagents. Progress and expected timelines depend on feed-back from vaccine manufacturers on the availability of antigen.

CBER is targeting mid-July for availability of reference antiserum. CBER expects to receive a supply of an egg-derived antigen for use as a reference antigen by mid-late July. Timing of reagent calibration and distribution to vaccine manufacturers will be dependent upon final availability of reference antiserum and antigen.

If reagents are not available to formulate inactivated vaccines for the initial clinical studies (Section 5.0), alternate methods may be considered.

3.0 Novel Adjuvants:

3.1 Adjuvant selection and availability: Because of the limited global capacity to produce sufficient novel influenza A (H1N1) vaccine antigen to immunize the global population and the possibility that a single dose of unadjuvanted vaccine may not yield an adequate immune response, antigen sparing techniques, such as

administration of reduced quantities of antigen with the oil-in-water adjuvants ASO3 (manufactured by GSK) and MF-59 (manufactured by Novartis) are being considered. There are currently no U.S. licensed influenza vaccines containing an adjuvant.

4.0 Novel influenza A (H1N1) Vaccine Regulatory Considerations

4.1 Regulatory Options: FDA has two options to make available a vaccine against novel influenza A (H1N1) virus: licensure and Emergency Use Authorization (EUA).

4.1.1 Licensure: A novel influenza A (H1N1) vaccine manufactured using the same process as U.S. licensed seasonal inactivated influenza vaccine, or a seasonal live attenuated influenza vaccine will be licensed for use as a strain change (but administratively submitted as a BLA). However, immunogenicity data to determine the appropriate antigen dose and dosing regimen will be requested, as described in the "FDA Guidance for Industry: Clinical data needed to support the licensure of pandemic influenza vaccines."

4.1.2 Emergency Use Authorization: Currently, no U.S. licensed vaccine contains the adjuvants MF-59 or ASO3. It is expected that a novel influenza A (H1N1) vaccine manufactured using the same process as U.S. licensed seasonal inactivated influenza vaccine but administered with MF-59 or ASO3 will be authorized for emergency use only. Section 564 of the Federal Food, Drug, and Cosmetic Act permits the FDA Commissioner to authorize the introduction into interstate commerce of a drug, device, or biological product intended for use in an actual or potential emergency. Products that are eligible for emergency use are those that "may be effective" in preventing serious or life threatening disease. Thus, the "effectiveness" standard for EUA is a lower level of evidence than the "effectiveness" standard used for vaccine licensure. Other statutory criteria for EUA of a product include a requirement that the known and potential benefits of the product outweigh the known and potential risks; and a conclusion that there is no adequate, approved, and available alternative to the vaccine for preventing the disease. A potential alternative product may be considered unavailable if there are insufficient supplies to meet fully the emergency need. If these criteria are met, the Commissioner can authorize the emergency use of an unlicensed novel influenza A (H1N1) virus vaccine or the unapproved use of an approved product. Under section 564 the Commissioner may establish conditions of authorization. These conditions include but are not limited to: requirements for information dissemination to healthcare providers; adverse event monitoring and reporting; data collection and analysis; and restrictions on product advertising, distribution and administration.

5.0 Clinical Studies

The following considerations for clinical studies are based on the premise that clinical trials can be completed in time to inform policy decisions regarding widespread use of novel influenza A (H1N1) virus vaccines. However, because surveillance and epidemiologic data may indicate that vaccination should be initiated before data from such clinical trials are available we recognize that the regulatory approach needs to be flexible and that policy decisions regarding vaccine formulation and use may have to be based on results from incomplete or smaller clinical studies or even in the absence of clinical data with novel influenza A (H1N1) virus vaccine.

5.1 Manufacturer Sponsored Studies – Concept Protocol:

Sponsors of U.S. licensed trivalent influenza vaccines have submitted proposals for clinical studies to support use of monovalent novel influenza A (H1N1) vaccines during a pandemic. The overarching principles for the design of clinical studies to generate immunogenicity data within a short time after availability of a vaccine are outlined in this section.

5.1.1 Objective: The objective of these initial clinical studies is to acquire sufficient data to support selection of the appropriate dose in relevant populations, and to obtain limited safety data.

5.1.2 Design: Studies should be randomized and double- or observer-blinded. Subjects will be administered two doses of vaccine. We have recommended vaccination on days 0 and 21; however, manufacturers may propose an alternate dosing regimen. Pediatric studies may include use of an active control arm. Adult studies may include a placebo or active control arm.

Enrollment should be stratified according to age (6m-9y [6m-35m, ≥3y-9y], ≥18-64y and ≥65years). Because the pediatric studies will require parental/guardian consent and pediatric subject assent in those unable to legally provide their own informed consent FDA has recommended separate adult and pediatric studies which can be conducted concurrently. FDA has not requested that manufacturers evaluate adolescents because we expect to extrapolate data from other age groups however; manufacturers who wish to obtain data in adolescents can include a subgroup in their pediatric study. This concept protocol does not include an evaluation of safety and immunogenicity in infants less than 6 months of age. These infants are recommended to receive a number of vaccines within 6 months of birth thus, any protocol to evaluate novel influenza A (H1N1) vaccine should be designed to evaluate the response to concomitantly administered vaccines.

Two of the manufacturers (Novartis and GSK) have proprietary oil-in-water adjuvants (MF-59 and ASO3, respectively) which have been evaluated in a number of clinical studies including studies with influenza vaccines. These manufacturers will include an evaluation of the utility of the adjuvant for dose sparing and enhanced immunogenicity in their clinical studies. While there may

be exceptions, in general, studies which include an adjuvanted arm(s) to evaluate dose sparing and enhanced immunogenicity may be conducted concurrently in the adult and pediatric age groups in order to have timely immunogenicity results to guide pediatric dose recommendations.

5.1.3 Population: Studies should enroll healthy subjects six months to 64 years of age as determined by physical exam and past medical history. Subjects age 65 years and older with chronic diseases may be enrolled if these subjects are able to comply with all study requirements.

5.1.4 Antigen dose: Each 0.25mL dose of inactivated seasonal vaccine administered to children 6m -35m of age contains 7.5 µg hemagglutinin (HA)/strain. Each 0.5mL dose of inactivated seasonal vaccine administered to children ≥3years of age and adults contains 15µg HA/strain. Because these antigen doses of seasonal vaccine are safe and efficacious, we recommend evaluation of 7.5µg and 15 µg HA of the novel influenza A (H1N1) in pediatric (6m-9y) and adult populations. In subjects ≥18 – 64 years of age and ≥65 years of age, we recommend evaluation of a higher dose such as 30µg HA.

Each 0.2mL dose of live intranasal influenza vaccine administered to persons 2y-49y of age contains $10^{6.5-7.5}$ FFU (fluoresecent focus units) of live attenuated influenza virus reassortants of each strain. We have recommended evaluation of this antigen dose.

5.1.5 Sample sizes: Within each age group the sample size estimates are based on the primary dose selection objective. A sample size of 100 subjects per arm is sufficient to provide a descriptive assessment of immunogenicity with a reasonable degree of confidence in that estimate. These studies will provide limited solicited local and systemic reactogenicity data as well as limited data on unsolicited adverse events over a longer time period.

Table 1 and 2 present the minimum evaluable subjects per age group and the dose of inactivated H1N1 antigen for pediatric and adult studies, respectively:

Table 1: Novel influenza A (H1N1) virus vaccine pediatric study: Sample size, hemagglutinin (HA) antigen dose and age groups**:

	Antigen dose		
Age range	**7.5 µg HA N**	**15 µg HA N**	**3.8 µg /7.5µg /15 µg HA* + adjuvant N**
6 m – 3 years	100	100	100/antigen dose
≥3 – 8 years	100	100	100/antigen dose

*Antigen dose-ranging arms, in combination with adjuvant, are provided as examples.
**A control arm, if used, should include at least 25 subjects per age group.

Table 2: Novel influenza A (H1N1) virus vaccine adult study: Sample size, hemagglutinin (HA) antigen dose and age groups**:

	Antigen dose			
Age range	**7.5 µg HA N**	**15 µg HA N**	**30 µg N**	**3.8 µg /7.5µg /15 µg HA* + adjuvant N**
≥18-64 years	100	100	100	100/antigen dose
≥ 65 years	---	100	100	100/antigen dose

*Antigen dose-ranging arms, in combination with adjuvant, are provided as examples.
** A control arm, if used, should include at least 50 subjects per age group

5.1.6 Safety Monitoring: Subjects should record age appropriate local and systemic reactogenicity for seven days after each vaccination. In addition, unsolicited adverse events, serious adverse events (SAEs), and deaths should be assessed for 21 days after each vaccination. Subjects should be followed for 6 months after the second vaccination for assessment of SAEs, deaths and new onset chronic medical conditions. If the study included evaluation of investigational adjuvants, subjects should be followed for 12 months after the second vaccine dose for occurrence of SAEs, deaths and new onset chronic medical conditions.

For studies that include evaluation of antigen formulated with an investigational adjuvant, we recommend safety laboratory evaluations at baseline and at early and late time points post-vaccination (e.g., days 7 -10, and 21).

5.1.7 Endpoints

Safety: For each antigen dose and age group:

- The incidence of solicited local and systemic events within 7 days of each vaccine dose
- Occurrence of unsolicited adverse events, serious adverse events (SAEs) and new onset chronic medical conditions throughout the entire study, including the 6-12 month follow-up period after the last dose of study vaccine

Immununogenicity: For each antigen dose and age group, 21 days post each vaccination:

- The proportion of subjects in each group with hemagglutination inhibition(HI) antibody titers ≥1:40
- Seroconversion rate: the proportion of subjects with a 4-fold rise in HI titer (pre HI <1:10, post ≥1:40, pre HI ≥1:10, post ≥4x pre)
- GMT

Exploratory immunogenicity endpoints to consider may include assessment of microneutralization titers and/or assessment of immune response endpoints at earlier timepoints (e.g., 3, 7, 10, and/or 14 days after vaccination.)

5.1.8 Criteria for Evaluation of Immunogenicity: The proportion of subjects achieving HI antibody titers ≥1:40 and seroconversion rates for subjects in each

dose and age group should be presented. The following criteria have been used to define an adequate response ("Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm).

For adults < 65 years of age (≥18-64y) and for the pediatric population (6m-8y, 6m-35m, 3y-8y):

- 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%.

5.2 NIH Sponsored Studies:

It is expected that NIH will sponsor some studies with novel influenza A (H1N1) virus vaccines. However, at this time the details of these studies are unclear. NIH will present its proposal for clinical trials with H1N1 vaccine at the July 23, 2009 VRBPAC.

6.0 Post Marketing Evaluation:

FDA and CDC together with other agencies in the Dept. of Health and Human Services (DHHS) are working to strengthen their ability to rapidly detect and evaluate potential safety signals following administration of novel influenza A (H1N1) virus vaccines. At the time of initial use of these vaccines there will be limited data from clinical studies evaluating safety. In addition, there is a possibility that some vaccines may be used under EUA (see Section 4.0). Because of these considerations, as well as the 1976 swine influenza vaccine experience, a number of methods to enhance surveillance for adverse events following administration of novel influenza A (H1N1) vaccines will be utilized.

Current plans are to monitor adverse events through reports to the Vaccine Adverse Event Reporting System (VAERS), as well as through diagnoses and related data in the Vaccine Safety Data (VSD) link system, the Department of Defense (DoD), Centers for Medicaid and Medicare Services (CMS), the Veterans' Health Administration (VHA), and other population based (MCO/HMO) health care organizations. DHHS is coordinating these activities. One challenge is linking adverse event data with vaccine administration data and

DHHS is exploring ways to improve the link between vaccine receipt and adverse event data.

FDA, CDC and their contractors are developing data mining tools, daily reports designed for novel influenza A (H1N1) vaccines, and vaccinee cards with vaccine and adjuvant details, including the manufacturer, lot numbers and date of administration, as well as "how to make a VAERS" report" information to enhance adverse event reporting.

FDA and CDC are planning safety surveillance systems which adapt to the various scenarios of public/private payment and administration of vaccines. Both agencies are working with states and on a national level to prepare multiple safety surveillance systems, which could be adapted to study sub-populations (e.g., young children, adolescents, pregnant women and the elderly) and to respond to the epidemiologic data identifying which populations should be targeted for early vaccination. Furthermore, FDA is also developing international collaborations for vaccine safety surveillance (standard case definitions, safety surveillance studies, communication, and risk management activities). FDA will be working with manufacturers and government agencies to coordinate surveillance plans. Given the limitations of clinical trial data prior to vaccine utilization, post-marketing or post-EUA surveillance studies are critical to evaluate safety and effectiveness of novel influenza A (H1N1) vaccines.

7.0 **July 23, 2009 VRBPAC Meeting:** During the meeting the committee will hear about the status of surveillance for and epidemiology of disease due to novel influenza A (H1N1) virus as well as the status of vaccine manufacture. FDA will review its plans to evaluate these products and facilitate the availability of novel influenza A (H1N1) virus vaccine. Other presentations will address vaccine procurement and clinical studies. The committee will have an opportunity to discuss these presentations.