

2009 H1N1 Influenza Issue Brief

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Licensure, Evaluation, and Adverse Event Monitoring of the 2009 H1N1 Influenza Vaccine

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In response to the emergence of the 2009 H1N1 influenza virus, public health officials have initiated the first mass vaccination campaign in the U.S. in more than 3 decades. As increasing supplies of vaccine have been made available, the safety of the vaccine has been questioned by many, and the resulting concern is reflected in opinion polls and in uptake of the vaccine. One source of concern has been the licensing process: the pandemic vaccines currently being distributed have been licensed using a process designed to limit the delay caused by the regulatory process. This rapid licensure process, which has been used for influenza vaccines in the past, could be undertaken only because the manufacturing processes for the seasonal and pandemic vaccines are nearly identical. Another source of concern has been related to lack of testing prior to licensure. Although no new clinical data were considered specifically for licensure of monovalent H1N1 vaccine, multiple NIH-sponsored and industry-sponsored clinical trials are now being conducted and will continue to provide data on vaccine safety through the spring of 2010. In addition, the safety of the pandemic vaccine will be scrutinized through a complex network of safety monitoring systems that are now in place and that focus on different geographic regions and populations.

Any informed discussion of safety requires an understanding of the licensing process for the 2009 H1N1 influenza vaccine and the various surveillance systems currently used by public health officials to monitor adverse events. This issue brief describes both.

Rapid Licensure Under the Strain-Change Supplemental

On September 15, 2009, the U.S. Food and Drug Administration (FDA) granted marketing licenses for 2009 H1N1 influenza vaccines to 4 pharmaceutical companies: CSL Limited, MedImmune LLC, Novartis Vaccines and Diagnostics Limited, and Sanofi Pasteur, Inc.¹ The vaccines from each of these companies were licensed under a “strain change” supplement to each manufacturer’s existing Biologic Licensing Agreement for the production of seasonal influenza vaccine. The strain change supplemental is a preexisting regulatory mechanism that is used annually to approve changes to the seasonal influenza vaccine, which includes an H1N1 influenza strain.

In licensing the vaccine by this mechanism, the FDA followed the consensus decision reached on July 23, 2009, by the Vaccines and Related Biological Products Advisory Committee (VRBPAC), an outside expert advisory group. In response to epidemiologic data suggesting the need for rapid initiation of vaccination programs, the VRBPAC supported the use of the strain change mechanism in the setting of an influenza pandemic.² Without the strain change mechanism, licensure could only follow completion of large clinical trials, the results of which would not be available until after the epidemic commenced, and possibly after it concluded.

Requirements for Licensure

Licensing vaccines under the strain change supplemental circumvents the need for new clinical trials because safety and efficacy of the vaccine for the new strain are judged based on the data acquired from annual clinical trials that test seasonal influenza vaccine. Data from those trials are included in the vaccines' package inserts that each company provides as supporting documentation.³⁻⁶ Licensing under the strain change supplemental can be acquired only if the dosing information and age groups for the monovalent H1N1 vaccine formulation match those of a manufacturer's seasonal influenza vaccines.

Consistent with the strain change licensing process, each company submitted data from clinical trials of their seasonal trivalent influenza vaccines. Of the vaccines approved, those produced by CSL, Novartis, and Sanofi Pasteur are "inactivated" vaccines administered via intramuscular injection and approved for persons aged 6 months and older. MedImmune's is a live attenuated influenza vaccine (LAIV) administered by intranasal inhalation and approved for persons aged 2 through 49 years.

On November 10, 2009, the FDA granted a fifth marketing license, via the strain change mechanism, to GlaxoSmithKline for its unadjuvanted, inactivated, injectable H1N1 vaccine that is approved for adults over the age of 18 years.⁷

GlaxoSmithKline is still awaiting licensure of its AS03-adjuvanted vaccine. An adjuvant is a compound that allows for enhanced stimulation of the immune system; inclusion of adjuvant can decrease the amount of viral antigen contained in each dose of vaccine. As a result, more doses of vaccine can be produced with the same amount of antigen. However, the FDA has never licensed an adjuvanted seasonal influenza vaccine, so licensure by the strain change mechanism is not possible.⁸

Preliminary Results of Vaccine Trials Influencing Policy

While not for the purpose of gaining FDA approval, a number of clinical trials testing the 2009 H1N1 influenza vaccine are now being conducted. Some have generated preliminary data that is guiding policies being established for vaccine usage. For example, prior to the availability of these results, public health officials assumed that 2 doses of vaccine would be necessary to elicit a protective immune response. Following release of this data, it became apparent that only 1 dose of vaccine is necessary to generate protective immunity for individuals over the age of 9 years. This welcome development made it possible to substantially increase the number of individuals who can be immunized even while vaccine supplies are limited. Overall, preliminary data indicates that the immunogenicity and safety profiles of the monovalent H1N1 influenza vaccine are comparable to those of the seasonal influenza vaccine.

The federal government is conducting a series of trials through the National Institutes for Allergies and Infectious Disease (NIAID), which is a division of the National Institutes of Health (NIH). These trials, listed in Table 1, below, are being carried out by researchers in a network of 8 academic medical centers known as the Vaccine and Treatment Evaluation Unit (VTEU). The goal of VTEU studies is to characterize the vaccine's immunogenicity and to determine optimal dose, number of doses, and vaccination schedule.⁹ Because these trials are intended to guide policy and not to provide data for licensure, their study designs may deviate from those typically required for FDA licensure. For example, some study designs may not include a placebo group, which would be required to demonstrate efficacy.

Table 1: VTEU/NIAID Clinical Trials of 2009 H1N1 Influenza Vaccine

Trial Name (start date; enrollment)	Preliminary Results (if available)
Sanofi H1N1 Influenza Vaccine Administered at 2 Dose Levels in Adult and Elderly Populations (08/09; N=408)	A single dose of vaccine (containing 15 mcg of antigen) appeared to generate a protective immune response in this population. [09/11/09. NIAID] ¹⁰
CSL H1N1 Influenza Vaccine Administered at 2 Dose Levels in Adult and Elderly Populations (08/09; N=450)	A single dose of vaccine (containing 15 mcg of antigen) appeared to generate a protective immune response in this population. [09/11/09. NIAID] ¹⁰
Sanofi H1N1 + TIV - Adults and Elderly (08/09; N=850)	Co-administration of the 2 influenza vaccines did not appear to impair the actions of either one. [10/09/09. NIAID] ¹¹
Peds Sanofi H1N1 Influenza Vaccine Administered at 2 Dose Levels (08/09; N=583)	A single dose of vaccine generates a protective immune response in children over the age of 9; 2 doses will be necessary for those under the age of 9. [09/21/09. NIAID] ¹²
Sanofi Pasteur, TIV + H1N1, Pediatric Population (08/09; N=650)	-
H1N1 Vaccine in Pregnant Women (09/09; N=120)	A single dose of vaccine (containing 15 mcg of antigen) appeared to generate a protective immune response in this population [11/02/09. NIAID] ¹³
Novartis H1N1 Vaccine in Pregnant Women (11/09; N=300)	-
H1N1 Vaccine at 2 Dose Levels in HIV Positive Adults (11/09; N=240)	-
Safety and Efficacy of an H1N1 Influenza Vaccine in People With Asthma (10/09; N=350)	-

Ongoing Industry Sponsored Clinical Trials

Individual pharmaceutical companies are also conducting studies of H1N1 vaccine safety and immunogenicity in infants, children, adults, and the elderly. Currently, there are 14 clinical trials being conducted in the U.S. (see Table 2, below), some of which are seeking to establish safety and efficacy of adjuvanted influenza vaccines, which are not currently licensed in the U.S. market.¹⁴ All of the studies were started between August and November of this year and will likely be completed in spring 2010.

Table 2: Pharmaceutical Industry Clinical Trials of 2009 H1N1 Influenza Vaccine

Sanofi Pasteur: Trial name (start date; enrollment)
<ul style="list-style-type: none"> • A Study of Different Formulations of an Adjuvanted A/H1N1 Pandemic Vaccine in Healthy Adults and the Elderly (08/09; N=450) • A Study of Different Formulations of an A/H1N1 Pandemic Vaccine in Healthy Children Aged 6 Months to 9 Years (08/09; N=450) • A Study of Different Formulations of an A/H1N1 Pandemic Vaccine in Healthy Adults and the Elderly (08/09; N=450)
GlaxoSmithKline: Trial name (start date; enrollment)
<ul style="list-style-type: none"> • Safety and Immunogenicity of H1N1 Vaccines in Adults Aged 18 Years and Older (09/09; N=1,260) • Safety, Immunogenicity, and Relative Efficacy of H1N1 Vaccines in Adults Aged 18 Years and Older (09/09; N=4,000) • Safety and Immunogenicity of H1N1 Vaccines in Children Aged 6 Months to Less than 9 Years of Age (09/09; N=480) • Safety and Immunogenicity of H1N1 Vaccine with Trivalent Inactivated Seasonal Influenza Vaccine in Adults (09/09; N=600)
Novartis: Trial name (start date; enrollment)
<ul style="list-style-type: none"> • Pivotal, Multicenter, Observer-Blind, Randomized Study of Influenza A (H1N1) 2009 Monovalent Subunit Vaccine with and without Adjuvant in Children Ages 6 to <36 Months (10/09; N=688) • Safety and Immunogenicity of A/H1N1-SOIV (Swine Flu) Vaccine with and without Adjuvant in Non-Elderly and Elderly Adults (09/09; N=2,720) • Safety and Immunogenicity of A/H1N1-SOIV (Swine Flu) Vaccine with and without Adjuvant in Children (3 to <9 Years) (09/09; N=1,360)
CSL Limited: Trial name (start date; enrollment)
<ul style="list-style-type: none"> • A Clinical Trial of CSL's 2009 H1N1 Influenza Vaccine (CSL425) in Healthy Adults in the USA (08/09; N=1,316) • A Clinical Trial of CSL's 2009 H1N1 Influenza Vaccine (CSL425) in a Healthy Pediatric Population in the USA (08/09; N=473)
MedImmune: Trial name (start date; enrollment)
<ul style="list-style-type: none"> • A Study to Evaluate the Safety of MEDI3414 in Adults (08/09; N=300) • A Study to Evaluate the Safety of MEDI3414 in Children (08/09; N=300)

Surveillance and Monitoring of Vaccine Safety: Overview of U.S. Vaccine Safety Monitoring Systems

To monitor safety of the 2009 H1N1 influenza vaccine, the federal government is leading an effort to establish and expand multiple systems for identifying and investigating adverse events that may follow vaccine administration.¹⁵ To coordinate this effort, a Federal Immunization Safety Task Force has been established comprising representatives from the FDA, Department of Health and Human Services (HHS), Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), Department of Defense (DoD), and Department of Veterans Affairs (VA).

As part of the effort to expand adverse event reporting systems, several databases housed in government, academia, and private industry are now being monitored in an attempt to characterize the incidence rates of adverse events. Those data sources are described below.

Vaccine Adverse Event Reporting System (VAERS): This nationwide joint venture of the CDC and FDA has been in operation since 1990, and the data it generates is an important source of information for public

health officials in evaluating vaccine safety. For instance, between 1991 and 2001, more than half a billion doses of inactivated influenza vaccine were administered in the U.S. During that same period, the VAERS reported 15,652 associated adverse events, the majority of which were fever and swelling at the injection site.¹⁶

Submission of adverse event data is voluntary and may be provided by healthcare providers and the general public. This system is deployed across a wide geographic and demographic base, and is able to detect rare events in near real time. Additionally, VAERS data can be analyzed to determine whether a specific sub-population is at increased risk for adverse events following vaccine administration, which has implications for policymakers and public health officials. Analysis of VAERS data also allows investigators to distinguish “true” vaccine-related adverse events from the coincidental medical emergencies that may be mistakenly linked to administration of the pandemic vaccine.¹⁵

Data from VAERS alone is not sufficient for determining a causal relationship between vaccination and a reported adverse event; follow-up epidemiologic investigations are required. To keep pace with increased usage of the VAERS over the coming months, the CDC and the FDA have announced plans to expand the capacity of VAERS and to create a dedicated workforce to manage the system and conduct follow-up investigations. Typically, the system is capable of processing 150 reports per day, and allows for public health follow-up of up to 20 of the most serious adverse events. The expanded VAERS will have the capacity to process up to 1,000 reports per day and follow up on 400 of the most serious cases.¹⁵

Vaccine Safety Datalink (VSD): This CDC-administered database links vaccine-specific healthcare information for approximately 9 million individuals enrolled in 8 managed care organizations. Information includes vaccination status, preexisting medical conditions, and demographic data. This near real time surveillance system is considered the backbone of the vaccine safety system in the U.S., as rapid cycle analysis (RCA) of its data is able to determine a casual relationship between vaccination and the incidence of an adverse event.¹⁵

Centers for Medicare and Medicaid Services (CMS): CMS houses healthcare information, including vaccination status, on approximately 35 million individuals over the age of 65. In concert with the FDA, CMS also has developed unique billing codes to distinguish pandemic from seasonal influenza vaccine administration, and intends to make this information available for surveillance purposes. However, its utility as a surveillance system will likely be limited given that the elderly are not among those prioritized for vaccination due to apparent preexisting immunity to the H1N1 virus.¹⁵

Post-Licensure Rapid Immunization Safety Monitoring (PRISM): This new partnership between HHS and the insurance industry will allow access to vaccine exposure and outcome data on approximately 10% of the U.S. population. This program establishes an active surveillance system that monitors the covered population for predefined adverse events, such as Guillain-Barré syndrome. In addition, PRISM uses combined data from the insurance industry and a public health surveillance system called the immunization information system (IIS) to rapidly determine rates of unanticipated adverse events.¹⁵

Defense Medical Surveillance System (DMSS): This DoD active surveillance system has access to the healthcare records, including vaccination history, for a substantial percentage of active duty defense personnel and can be used to determine a temporal relationship between vaccination and the incidence of an adverse

event. For use during the 2009 H1N1 pandemic, this system is being linked with the VSD to increase the system's specificity and sensitivity (a.k.a. signal strengthening).¹⁵

Department of Veterans Affairs (VA): A new partnership between the VA and FDA has been established to gather and analyze data on approximately 1 million VA patients in order to gain insight into the effects of the pandemic vaccine in a primarily elderly, inpatient population. Like other active surveillance systems, the data generated by this system will be used to detect the incidence of pre-defined adverse events of interest. Data from the VA healthcare system has been used in the past to study incidence rates of adverse events from medications and is well suited to the task of signal strengthening.¹⁵

Real Time Immunization Monitoring Systems (RTIMS): The RTIMS system is an automated, internet-based, passive surveillance system developed at the Johns Hopkins University to complement the VAERS. This system specifically monitors post-vaccination outcomes among 3 of the vaccine priority groups: pregnant women, healthcare workers and school children. Data is entered into the RTIMS system by vaccinees at 1 day, 1 week, and 6 weeks post-immunization to determine rates of adverse events, which will then be reported to the VAERS.¹⁵

Clinical Immunization Safety Assessment (CISA) Network: This association of 6 academic medical centers (Johns Hopkins University, Boston University, Stanford University, Vanderbilt University, Columbia University, and Northern California Kaiser Permanente) has a collaborative relationship with the CDC and provides expert advice and analysis on issues relating to vaccination safety. These subject matter experts are often involved with the follow-up of particularly serious VAERS reports, including collection and analysis of biologic material from individuals to determine the cause of the event. CISA also maintains a repository of its findings.¹⁵

Vaccines and Medications in Pregnancy Surveillance System (VAMPSS): This system was established through a collaborative effort between the Organization of Teratology Information Specialists (OTIS), the Slone Epidemiology Center (SEC) at Boston University and, the American Academy of Allergy, Asthma, and Immunology (AAAAI) to collect data on the health effects of pandemic vaccine administration on maternal and fetal health. Investigators from this partnership will conduct both prospective and retrospective case-control studies to determine the incidence of a number of complications of pregnancy. However, it will be difficult for this system to produce data that is immediately actionable due to the time lag inherent in following groups of vaccinated and unvaccinated women through their pregnancies.¹⁵

H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRWG): A special working group of the National Vaccine Advisory Committee (NVAC) that commenced monitoring activities on November 2, 2009, will add another layer of oversight by offering independent, expert analysis of the data generated by the multiple feeds to the adverse reaction surveillance systems and by advising the federal government on issues relating to vaccine policy.¹⁷

Conclusion

The licensure process for the 2009 H1N1 influenza vaccine and the safety monitoring systems reflect a commitment on the part of regulatory agencies and the public health community to ensuring that the 2009 mass immunization campaign emphasizes vaccine safety. Given that the 2009 H1N1 vaccine is manufactured

in the same manner as seasonal influenza vaccines, it seems reasonable to base an assessment of its safety on the long-standing and consistent safety profile of seasonal influenza vaccines. Beyond that, the large number of ongoing clinical trials and the number of surveillance systems currently employed to monitor adverse events will provide continual data on safety and will continue to inform public policy as the immunization campaign continues.

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