

H5N1 Influenza Virus Vaccine, A/Vietnam/1203/2004 (Clade 1) 90 mcg/ml

VRBPAC Briefing Document

Version 1.0

29 January 2007

Appendix 1: Definition of Safety Parameters (as defined in the DMID Protocol 04-063)..... 37

Appendix 2: Study Publication in NEJM 42

Appendix 3: Synopsis of the Final Integrated Clinical/Statistical Report..... 51

Appendix 4: Summary of Benefit Risks..... 67

List of Abbreviations

A/H5N1	Influenza A Virus of the H5N1 Subtype
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ASPR	Assistant Secretary for Preparedness and Response
BLA	Biologic License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
HA	Hemagglutinin
Hgb	Hemoglobin
HPAI	Highly Pathogenic Avian Influenza
ICH	International Conference on Harmonisation
IM	Intramuscular
IN	Institutional Normal
IND	Investigational New Drug application
LLOQ	Lower Limit of Quantitation
mcg (µg)	Micrograms
Mfg	Manufacturing
mL	Milliliter
NA	Neuraminidase
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
Plt	Platelets
POC	Point of Care

PSURs	Periodic Safety Update Reports
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
ULN	Upper Limit of Normal
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WBC	White Blood Cells
WHO	World Health Organization

1 Background

The potential for a human influenza pandemic is a current public health concern with an immense potential impact. Preparing for the next influenza pandemic requires support and collaboration from multiple partners. On 01 November 2005, the President of the United States requested \$7.1 billion in emergency funding for the *National Strategy for Pandemic Influenza*, of which \$6.7 billion was designated for the US Department of Health and Human Services (DHHS). In May 2006, the *National Strategy for Pandemic Influenza Implementation Plan* was released. [1] It translated the *National Strategy for Pandemic Influenza* into more than 300 actions, timelines, and metrics for Federal departments and agencies and set clear expectations for State and local governments and other non-Federal entities. One of the Federal priority actions was to “Accelerate the Development of Medical Countermeasures” and included these efforts:

- Establish stockpiles of vaccine and antiviral medications
- Advance technology and production capacity for influenza vaccine
- Develop rapid diagnostics.

Cascading from the National Strategy and National Implementation Plan, one of the key components of the DHHS plan called for increasing capacity to produce pandemic influenza antivirals and vaccines, and increasing stockpiles of these countermeasures. Specific strategic goals for pandemic medical countermeasures are displayed in [Table 1](#).

Table 1: DHHS Pandemic Medical Countermeasure Goals

Vaccine Goal #1	To establish and maintain a dynamic pre-pandemic influenza vaccine stockpile sufficient for 20 million persons (at 2 doses/person): H5N1 vaccine stockpiles
Vaccine Goal #2	To provide pandemic vaccine to all US citizens within 6 months of a pandemic declaration: 600 million doses pandemic vaccine
Antivirals Goal #1	To provide influenza antiviral drug stockpiles for pandemic treatment of 25% of US population: 75 million treatment courses
Antivirals Goal #2	To provide an influenza antiviral drug stockpile for strategic limited containment at onset of pandemic: 6 million treatment courses
Diagnostics Goal #1	To develop new high throughput laboratory and Point of Care (POC) influenza diagnostics for pandemic virus detection

The Pandemic Influenza Medical Countermeasure Program now includes 25 contracts obligating over \$3 billion. [Table 2](#) illustrates the multi-pronged approach and diversified portfolio of programs that have been established to help achieve the Implementation Plan’s medical countermeasure goals.

Table 2: DHHS Pandemic Influenza Medical Countermeasure Programs

	Vaccines	Antivirals	Diagnostics
Advanced Development	<ul style="list-style-type: none"> •Cell-based •Antigen-sparing •Next Generation •Egg-based Supply 	Peramivir	<i>High Throughput</i> <ul style="list-style-type: none"> • Point of Care • Clinical Lab
Acquisitions	H5N1 Vaccine Stockpiles	<i>Tamiflu[®] & Relenza[®]</i> <ul style="list-style-type: none"> • Federal Stockpiles • State Stockpiles 	
Infrastructure Building	<ul style="list-style-type: none"> •Retrofit Existing Mfg Facilities •Build New Cell-based Mfg Facilities 		

Vaccines

Vaccines are the optimal way to control the spread and associated morbidity and mortality of seasonal epidemics or pandemics. Developing vaccines for a pandemic may be divided into two categories: those that are developed against strains of animal influenza viruses that have caused isolated infections in humans, which may be regarded as “pre-pandemic” vaccines; and those that are developed against strains that have evolved the capacity for sustained and efficient human-to-human transmission (“pandemic” vaccines). Because emergence in human populations necessarily reflects genetic changes within the pandemic virus, pre-pandemic vaccines may be a good or poor match for – and offer greater or lesser protection against – the pandemic strain that ultimately emerges. Thus, the DHHS strategy is to simultaneously stockpile a limited amount of pre-pandemic vaccine; build vaccine manufacturing capacity so that pandemic vaccine can quickly be produced should a pandemic occur; and explore approaches utilizing adjuvants to enhance the likelihood that a vaccine administered prior to a pandemic will provide useful protection during a pandemic. Furthermore, this approach will strengthen and integrate both the seasonal and pandemic influenza preparedness needs.

Vaccines – Acquisitions

The Assistant Secretary for Preparedness and Response (ASPR) currently has a vaccine acquisition program that includes four projects with six contracts and obligations over \$500 million to procure pre-pandemic vaccine (Table 3).

Although much has been accomplished, continued vigilance and preparation are needed to be ready for Influenza – seasonal epidemics and pandemics.

With the re-emergence of highly pathogenic avian H5N1 influenza virus in poultry and humans in late 2003 in Asia, the National Institutes of Health (NIH) and DHHS in 2004 awarded contracts to Sanofi Pasteur, Inc., Swiftwater, PA (formerly Aventis Pasteur) to

develop and manufacture an egg-based inactivated split H5N1 vaccine at pilot scale for clinical investigation and at commercial scale for stockpiling of pre-pandemic vaccines. With the results of clinical trials conducted by the NIH and others, DHHS has supported sanofi pasteur and other U.S.-licensed influenza vaccine manufacturers to develop their H5N1 vaccine candidates further and manufacture bulk vaccine product using the commercial scale and licensed product process.

Manufacturing these pre-pandemic vaccines not only provides the industry experience in producing novel influenza vaccine candidates at a commercial scale, but also provides a foundation for pre-pandemic vaccine stockpiles. In the early stages of a severe pandemic, and before a well-matched vaccine is available, pre-pandemic vaccines may be used in selected populations to mitigate disease, support essential operations, and maintain social and economic systems.

Table 3: DHHS H5N1 vaccine acquisition projects

Projects	Contracts	Award	Duration	Goals/Results
H5N1 Vaccine Clade 1 - 2004	1	\$21M	2004-08	Provide 0.47 M doses at 90 µg/dose
H5N1 Vaccine Clade 1 - 2005	2	\$243M	2005-08	Provide 8.0 M doses at 90 µg/dose
H5N1 Vaccine Clade 2 - 2006	3	\$241M	2006-08	Provide 4.9 M doses at 90 µg/dose
H5N1 Vaccine 2007	TBD	TBD	2007-09	Provide doses for pre-pandemic stockpile (H5N1)

Currently, 1.3 million doses of H5N1 Influenza Virus Vaccine (90 µg/dose) have been filled in vials. More than 6 million doses (90 µg/dose) of this H5N1 Influenza Virus Vaccine remain in bulk form and await instructions for formulation into final vaccine vials. Additionally, approximately 5 million doses of this H5N1 Influenza Virus Vaccine are currently under production.

Using FDA “strain change” guidance on pandemic vaccine manufacturing, DHHS has encouraged sanofi pasteur and other influenza vaccine manufacturers to seek U.S.-licensure of their H5N1 vaccine products based on their currently licensed influenza vaccine products and extends the Department’s policy on the preferred usage of licensed medical countermeasures for a pandemic like the licensed influenza antiviral drug being stockpiled.

Sanofi Pasteur, Inc. in meeting the US Government’s challenge has developed and has also applied for licensure of the 90 µg H5N1 Influenza Virus Vaccine. This vaccine is a part of stockpile plans within the *National Strategy on Pandemic Preparedness*. The application for licensure is another step in assuring stockpiles of vaccine are available in the event of pandemic declaration.

2 Introduction

On 27 February 2007, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet to review the Biologic License Application (BLA) for H5N1 Influenza Virus Vaccine (A/Vietnam/1203/2004 [Clade 1] 90 µg/mL). H5N1 Influenza Virus Vaccine is a monovalent split virus vaccine containing 90 µg/mL of A/H5N1 HA manufactured by Sanofi Pasteur Inc, Swiftwater, PA.

H5N1 Influenza Virus Vaccine contains thimerosal as a preservative and the 1.0 mL dose is administered intramuscularly in a two dose regimen, approximately 28 days apart. The proposed indication for H5N1 Influenza Virus Vaccine is for active immunization in healthy, adult population 18 to 64 years against the avian influenza A viruses of the H5N1 subtype.

Given that vaccination remains a critical defense against the threat of avian influenza, the National Institute of Allergy and Infectious Diseases (NIAID) took the lead working with licensed manufacturers to generate clinical data that would help support the overall development of safe and effective vaccines against the H5N1 strain. In May 2004, NIAID awarded a contract to sanofi pasteur for the production of a small scale investigational lot of H5N1 Influenza Virus Vaccine for human studies that would be conducted by NIAID. Under the NIAID contract, sanofi pasteur was tasked with producing H5N1 Influenza Virus Vaccine following the same methods used to produce the seasonal influenza vaccine, Fluzone[®]. In that same year, an investigational new drug (IND) application for the pandemic influenza vaccine product was opened by the NIAID. Over the subsequent three years, a clinical development program in adults, elderly and children was initiated and conducted by NIAID. The results of a clinical trial conducted in adults with H5N1 Influenza Virus Vaccine 90 µg were published in the *New England Journal of Medicine* (NEJM) by Dr. John J. Treanor and colleagues. (Treanor, et.al. 2006, [1])

Following the NEJM publication, the US Department of Health and Human Services (DHHS) requested that sanofi pasteur seek licensure of the vaccine. During a pre-supplemental Biologics License Application (BLA) meeting, Center for Biologics Evaluation and Research (CBER) requested a re-analysis of the serological results by sanofi pasteur. In addition, sanofi pasteur was instructed to submit a separate BLA for a stand alone product independent of the Fluzone[®] labeling. The BLA was submitted to the Food and Drug Administration (FDA) on 13 October 2006.

In December 2006, NIAID and sanofi pasteur were notified of the 27 February 2007 VRBPAC meeting to discuss the pending application of H5N1 Influenza Virus Vaccine. This briefing document provides information regarding the epidemiology of avian influenza, the mechanism for immunologic protection, clinical development program, clinical data, and provides the concepts behind pharmacovigilance planning in a pandemic.

3 Influenza Pandemic

An influenza pandemic occurs when a novel influenza virus emerges against which the vast majority of the world's population has no immunity. This has been observed only with influenza A viruses and is due to the emergence of a new antigenic variant (antigenic shift) caused by substitution within the hemagglutinin (HA) antigen on the surface of the virus, with or without a concomitant change in neuraminidase (NA), the other surface antigen. If such a virus demonstrates the ability to transmit efficiently from person to person, the result is a global outbreak of the disease that affects a high percentage of individuals in a short period of time and is likely to cause substantially increased morbidity and mortality in all countries of the world.

Most people are immunologically naïve to the novel virus and are therefore more susceptible to influenza infection. The first identifiable influenza pandemic in more than 300 years of detailed records of human influenza occurred in 1847. [1] Since 1847, there have been 3 influenza pandemics: [4]

- The "Spanish influenza", between 1918 to 1919, was due to an A/H1N1 virus related to porcine influenza
- The "Asian influenza", between 1957 to 1958, was due to an A/H2N2 virus
- The "Hong Kong influenza", between 1968 to 1969, was due to an A/H3N2 virus.

The impact of pandemic influenza is better appreciated when compared with the more familiar patterns associated with inter-pandemic disease. Between pandemics, influenza is characterized by extremely low viral transmission in the summer [5] followed by an annual increase in winter seasonal activity. [6] The winter epidemic is variable in intensity and duration, usually produces clinically recognizable disease in the population.

In contrast, influenza pandemics are not limited to the winter season, and are characterized by several waves of infection following the emergence of the virus. [4] In the 1918-1919 pandemic, the first wave occurred in spring 1918 in the USA. The second began in August 1918 and had a higher mortality rate. The third appeared in spring 1919. The reason for these waves of infection is unclear. During the successive waves, virus virulence increased. [4] These characteristics have important implications for planning against the next pandemic.

The pandemics of the 20th century occurred at intervals ranging from 11 to 39 years. It is now approximately 39 years since the last pandemic in 1968. Pandemic influenza can occur at any time of year and may spread rapidly throughout the world. The three influenza pandemics of the 20th century demonstrate what can be expected when the next one occurs.

The estimated clinical attack rate was remarkably similar in the last three pandemics: about 25% of the world's population. The 1918 to 1919 pandemic killed 50 to 100 million people versus around one million people in 1957 to 1958 and 800,000 people in 1968 to 1969.

Between pandemics, the vast majority of influenza-related deaths occur in the elderly, although infants and young children may also succumb. A similar pattern of age-specific

mortality occurred in the first wave of 1918 pandemic influenza. However, during the second wave, this pattern changed radically. Mortality among 0 to 4 year-olds rose considerably, but death rates in all other age groups less than 40 years old increased more dramatically, peaking at almost 15% in the 25 to 29 year age group. In contrast, in those over 50 years old, death rates were lower in the second wave than in the first and were especially low in the over 80s. [4]

Pandemic influenza is characterized by the sudden onset of severe typical influenza symptoms: high fever, headache, myalgia, arthralgia, anorexia, nausea, vomiting and cough lasting two to four days. Although most patients recover, some die rapidly due to tracheo-bronchitis associated with dyspnoea. After initial recovery, some patients subsequently develop pneumonia.

Although antiviral drugs may be beneficial, vaccines will form the main prophylactic measure against pandemic influenza and will play a major role in the plans to prepare for a pandemic. The World Health Organization (WHO) Influenza Surveillance Program provides representative influenza viruses for antigenic and genetic analysis and from this information, the WHO is able to make recommendations on vaccine composition. [7] The WHO reference laboratories, such as the Center for Disease Control and Prevention (CDC) Influenza Branch, have a key-role to play in detecting new influenza viruses that are likely to cause pandemics and advising on suitable vaccines strains and their use. As of 30 January 2007, the WHO current pandemic alert level is 3 which is defined as no or very limited human-to-human transmission. [7]

Conventional inactivated influenza vaccines may be unsuitable against pandemic influenza when given as a single dose. In naïve populations, the 15 µg-dose of a conventional split vaccine without adjuvant is poorly immunogenic. Recent studies of “pandemic like” vaccines have shown the advantages of adjuvanted vaccines and a two dose schedule, especially in unprimed individuals. [9, 10, 11, 12, 13, 14]

In order to accelerate the development of the pandemic vaccine, the European Committee for Proprietary Medicinal Products (CPMP) has developed guidelines for licensing pandemic influenza vaccines. [15, 16] The guidelines recommend the development of a “mock-up” pandemic vaccine, produced from a novel influenza virus. Speed in vaccine development is vital and this guideline provides the basis for a fast-track licensing procedure for pandemic vaccines within the European Union. The procedure involves the submission and approval of a core pandemic dossier during the inter-pandemic period, followed by a fast-track approval of the pandemic vaccine, based on the submission of pandemic variation.

The Center for Biologics Evaluation and Research has also issued a draft guidance regarding the clinical data required for licensure of a pandemic vaccine. It recommends that licensure of pandemic influenza vaccines may be sought either as a supplement to an existing BLA or as a new BLA using the accelerated approval regulations (21 CFR Part 601 Subpart E). Clinical trials are needed to support the appropriate dose and regimen of the pandemic influenza vaccine.

These trials are encouraged to include an assessment of immunogenicity and safety. Although this draft guidance is not considered binding, it outlines specific criteria for immunogenicity and safety as indicated below:

1. Immunogenicity:

Data to support the selected dose and regimen should be based on the evaluation of immune responses elicited by the vaccine. The hemagglutination inhibition (HI) antibody assay has been used to assess vaccine activity and may be appropriate for the evaluation of the pandemic influenza vaccine. Appropriate endpoints may include: (i) the percent of subjects achieving an HI antibody $\geq 1:40$, and (ii) rates of seroconversion, defined as a four-fold rise in HI antibody titer post-vaccination.

The geometric mean titer (GMT) should be included in the results. These data and the 95% confidence intervals (CI) of the point estimates of these evaluations should be provided with the BLA clinical supplement.

Considerable variability can be introduced into the laboratory assay used to measure HI antibodies as a result of a number of factors including differences in viral strains, red blood cell types, and the presence of non-specific inhibitors in the assay medium.

Thus, suitable controls and assay validation are important for interpreting HI antibody results. Other immunologic assays, such as the microneutralization assay, might also be used to support the approval of a pandemic influenza vaccine as a clinical supplement to the BLA.

2. Safety:

Local and systemic reactogenicity events should be well defined in all age groups for whom approval of the vaccine is sought. Appropriate grading scales to describe the severity of the adverse events should be included in the study protocol.

Serious adverse events should be monitored and collected for all subjects throughout the duration of the studies. The protocol should include a clinic visit or telephone contact at least six months post-vaccination to ascertain additional serious adverse events and new onset of chronic illnesses that may have occurred in the interim. [17]

The data submitted in the BLA meet the requirements as outlined in the draft guidance.

4 Avian Influenza H5N1 Disease

Avian influenza is a contagious disease caused by viruses that normally infect only birds and less commonly, pigs. An outbreak of avian influenza, especially of the highly pathogenic form can be devastating for the poultry and farming industry. The Avian influenza A viruses of the H5N1 subtype are causing widespread infections in bird populations throughout Southeast Asia, with spread into Central Asia, Africa, and Europe. [18]

The disease can spread from country to country through migratory birds, including wild waterfowl, sea birds, and shore birds. There have been a number of instances of transmission of these viruses to humans, resulting in severe disease or death. [19]

These viruses possess a new H5 subtype of hemagglutinin, against which at present there is little immunity in human populations. The A/H5N1 viruses have the potential to cause extremely severe respiratory illness in humans, and have been known to repeatedly “jump the species barrier”. Many of the viruses isolated from humans have been found to be genotypically resistant to the adamantanes, [20] (antiviral agents) and resistance to oseltamivir (Tamiflu[®]) has also been documented. [21]

Although human-to-human transmission appears at present to be rare, [22] a recent bird-flu outbreak in an Indonesian village where seven family members died, has raised the level of concern that the virus may be able to pass directly between people. With no animal identified as yet as the source of infection, the family cluster in Indonesia raises the suspicion of human-to-human transmission. [23] There is also a possibility that in this current situation, avian and human influenza viruses could exchange genes if an individual was simultaneously infected with viruses from both species. This could give rise to a new subtype of the influenza virus to which humans would not have natural immunity, and could result in the next influenza pandemic in humans.

As of 11 January 2007, the cumulative number of laboratory-confirmed human cases of Avian Influenza A-(H5N1) reported to the World Health Organization (WHO) was 264, including 158 (59.85%) deaths in human adults and children in Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Thailand, Turkey, and Vietnam. [24]

The development of an effective vaccine against influenza A (H5N1) virus is a matter of considerable urgency.

