INFORMATION PAPER

DASG-HCA
9 May 2006

SUBJECT: Status of National Avian Influenza A/H5N1 Vaccine Efforts

1. Purpose. To describe the characteristics, quantities, and dates of availability of several vaccines under development to prevent influenza A/H5N1.

2. Executive Summary. The Department of Health & Human Services (DHHS) has several influenza A/H5N1 vaccines in various stages of development. The most-advanced vaccine, called "1203," is made from virus isolated in Vietnam in 2004. The Department of Defense (DoD) purchased ~ 2.4 million doses of this vaccine, currently stored by the manufacturer. This product is being held in bulk, pending studies that may increase the yield, except for 1.3 million doses to be bottled in June 2006. DHHS also is holding its "1203" vaccine in bulk for the same reason. Other nontraditional types of influenza vaccine are also under study.

3. Facts.

a. Status of "1203" Vaccine.

(1) Description. DHHS contracted with Sanofi Pasteur to use its traditional egg-based production methods to produce A/H5N1 vaccine for NIH-sponsored clinical trials. The seed virus for this vaccine, named A/Vietnam/1203/04 or "1203," was produced using reverse-genetic technology at Saint Jude Children's Research Hospital in Memphis, based on a viral isolate from a young boy who died of A/H5N1 infection in Vietnam in 2004. Clinical trials showed two immunizations 28 days apart with a 90-mcg dose of hemagglutinin antigen are needed to induce presumptive immunity (i.e., hemagglutination-inhibition titers $\geq$ 1:40). This degree of antibody response would typically protect about 70% of adults from influenza A/H1N1 or A/H3N2 infection. The standard 15-mcg dose was not sufficiently effective.

(2) Quantity. In late October 2005, DHHS received bulk "1203" vaccine in a quantity representing 3.3 million doses @ 90 mcg/dose. Bulk "1203" vaccine designated for DoD was also produced: 2.4 million doses @ 90 mcg/dose @ $30 per bulk dose. This product passed quality-assurance tests. DHHS and DoD will keep their vaccine in bulk, pending studies that could increase the vaccine's yield. Bulk vaccine must be stored by the manufacturer (i.e., in Pennsylvania). Approximately 1.3 million doses will be bottled in June 2006.

(3) Additional Yield. It may be possible to increase the yields described above, perhaps 2- to 24-fold, by adding an adjuvant (e.g., aluminum), to increase the immune response to the vaccine. If so, this bulk could yield millions of additional doses. But adjuvants cannot be added to vaccine after packaging into vials.

(4) License Status. Because the "1203" vaccine was produced using Sanofi Pasteur's licensed process and plant in Swiftwater, PA, it could be licensed by the Food & Drug Administration (FDA) relatively simply, via a document called a supplement to the influenza vaccine's Biological License Application (i.e., BLA Supplement). Under current timelines, in the absence of a pandemic, FDA could consider a licensing request for the "1203" vaccine by fall 2006. If the vaccine is needed before FDA licenses it, the vaccine could be administered under an Emergency Use Authorization (EUA), a provision of the Project BioShield Act.

(5) Specifications. Like Sanofi Pasteur's licensed *Fluzone*-brand of influenza vaccine, "1203" vaccine would be injected intramuscularly, as a split-virion preparation, with phosphate-buffered saline as a solvent. The dose volume would be 1 ml, with the vaccine packaged in 5-ml vials, stored in a refrigerator, containing trace amounts of gelatin (rarely, an allergen), with thimerosal as a preservative. The vaccine may be stable for 18 to 24 months.

(6) Industrial Capacity. Today, Sanofi Pasteur can produce "1203" vaccine only when not producing the regular supply of seasonal influenza vaccine. Sanofi Pasteur expects to open a new egg-based facility in 2008 with several times its present capacity. At that time, the current facility could be devoted to avian influenza vaccine work.

b. Aluminum-Adjuvanted Vaccine. A small quantity of "1203" vaccine has been combined with aluminum hydroxide as an adjuvant, to see if this combination can reduce the viral antigen dose needed to confer immunity. Clinical trials of this product began in February 2006, with results expected in July 2006. These trials will assess 3.75, 7.5, 15, and 45 mcg doses. Aluminum-adjuvanted influenza vaccines were used in the United States in the late 1970s, but not recently. FDA would consider these new vaccines, requiring clinical trials in several hundred volunteers before licensing.

c. Clade 2. Some isolates of A/H5N1 virus appear different to the human immune system, unlike the "1203" strain. These isolates have been found in Indonesia, Mongolia, and Turkey, and are referred to as "clade 2." Antibodies that neutralize the "1203" virus do not neutralize H5N1 clade-2 viruses. This suggests that close matching of a vaccine strain to a circulating pandemic strain is important for protection.

4. Implications. DoD could increase the yield of its "1203" vaccine, by keeping it in bulk, pending results of the aluminum-adjuvant studies in spring 2006. If sustained human-to-human transmission occurred before spring 2006, the bulk could be filled into vials, packaged, and released within approximately 4 weeks. Given that two doses are typically needed to immunize against novel influenza viruses, the "1203" vaccine could represent dose #1 for 2.4 million people, with dose #2 (yet to be produced) consisting of a slightly different vaccine from a pandemic strain of virus that does not exist yet.

LTC Stephen M. Ford/DASG-HCA/703-681-5101

Approved by: COL Grabenstein