Leadership, Accomplishment, Public Confidence

Sanofi Pasteur and the A (H1N1) Pandemic

About Sanofi Pasteur

Sanofi Pasteur is the largest company in the world devoted entirely to vaccines – producing vaccines against 20 infectious diseases. In 2008, the company provided more than 1.6 billion doses of vaccine, making possible immunization of more than 500 million people worldwide. The company has more than 3,000 employees in the United States and 11,000 worldwide – and operates major facilities in France, Canada and in Swiftwater, Pennsylvania.

Sanofi Pasteur is also the world’s largest manufacturer of influenza vaccine – producing approximately 45 percent of the U.S. influenza vaccine supply, and 40 percent of the worldwide supply. In 2008, the company produced 170 million doses of seasonal influenza vaccine, and in 2009 the company expects to produce up to 180 million doses for use worldwide, including more than 50 million doses of seasonal influenza vaccine for U.S. distribution.

With two manufacturing facilities at the Pennsylvania site capable of producing both seasonal and pandemic A (H1N1) vaccines, Sanofi Pasteur is the only company that manufactures inactivated (injectable) influenza vaccine in the United States.

Pandemic Preparedness

Sanofi Pasteur has worked closely with the U.S. Department of Health and Human Services (HHS) and other public health agencies to develop and produce a safe and effective A (H1N1) vaccine as rapidly as possible.

Our pandemic vaccine preparedness effort began in 2004, when we began working with HHS on early plans for such an event. We were the first company to develop a proven, large-scale manufacturing process for an H5N1 avian influenza vaccine – and we remain the only manufacturer with a licensed H5N1 vaccine in the United States. Our H5N1 preparations laid the groundwork for our response to the A (H1N1) virus.

Producing, packaging, filling and distributing two influenza vaccines – the seasonal and the A (H1N1) – simultaneously, has presented unprecedented and complex challenges. But Sanofi Pasteur understood the importance of continuing to deliver needed supplies of seasonal influenza vaccine while also helping governments make certain that sufficient supplies of the A (H1N1) vaccine are available.

Today, more than 2,000 people at our Pennsylvania facility are in some manner involved in responding to the pandemic through development, production and distribution of the A (H1N1) vaccine. These workers are dedicated to producing the largest number of A (H1N1) vaccine doses in the shortest amount of time, while ensuring vaccine safety and compliance with legal and regulatory requirements. Our production facilities are
operating 24 hours a day, seven days a week – and we expect to produce and distribute over 75 million doses of A (H1N1) vaccine while also producing more than 50 million doses of seasonal vaccine.

**Egg-based technology for producing influenza vaccine**

Recent reports of A (H1N1) vaccine shortages have spurred some to question whether the current influenza vaccine manufacturing process might be outdated. Ironically, it is largely because the vaccine manufacturing process is so well established that the vaccine’s safety profile is so well defined.

In fact, it is the same process that has been used year after year to manufacture seasonal influenza vaccines, which contain different viral strains in different years. Fortunately, egg-based production of influenza vaccine has an excellent track record, with 1.5 billion doses of seasonal influenza vaccine produced by Sanofi Pasteur and administered worldwide over the last 40 years.

Of course, there is always room for improvement, and we continually seek ways to improve our processes -- but never at the expense of quality.

The manufacture of an influenza vaccine is a complicated process, involving many steps that take months to complete. These steps help to ensure a vaccine’s potency, purity and consistency. The egg-based process of growing antigen is only one step in that process. It is a step that cannot be rushed – and it is a process that can only begin after the seed virus is isolated and sent to us by the U.S. Food and Drug Administration.

And no matter what production method is used, all vaccines must undergo rigorous quality control and safety testing -- a rigorous process that accounts for approximately 85 percent of production time.

The egg-based vaccine production method we currently utilize is a technologically sophisticated and advanced process that has proven adaptable to emergency situations such as the pandemic we are now experiencing. This has not stopped us from containing research into ways to improve all aspects of vaccine production, including cell culture technology. But we believe egg-based production is likely to remain the most reliable, productive and practical method of mass producing influenza vaccines for many years to come.

**Timeline for Vaccine Delivery**

In producing a complex biological product there is always an element of uncertainty regarding the production schedule. This is true regardless of the technology that is used. Although Sanofi Pasteur is on track to provide HHS with the A (H1N1) vaccine quantities that were requested, the vaccine’s availability was initially delayed because the virus strain’s yield started out significantly lower than standard. Lower yielding new strains are not unusual, even for seasonal influenza vaccine; however, the initial A (H1N1) yields were exceptionally low.
Fortunately, we were able to utilize our expertise to optimize the productivity of the seed virus and have been successful in bringing yields very close to seasonal influenza vaccine standards. Thus, we do not anticipate the strain yield to be a factor impacting future production schedules.

Sanofi Pasteur began shipping A (H1N1) vaccine on September 29, 2009, which was earlier than planned. By early November, the company had shipped 16.7 million doses – and we plan to ship several million more doses in each of the weeks ahead.

We have orders from HHS for 75.3 million doses of bulk antigen for anticipated delivery between October and December, and although we are still awaiting final direction on the formulation and fill of the final portion of the bulk antigen, we are on track with all orders received thus far and fully anticipate we will produce all 75.3 million doses as requested by the U.S. government.

**Immunogenicity and Safety**

The U.S. Food and Drug Administration licensed the *Influenza A (H1N1) 2009 Monovalent Vaccine* as a strain change to the seasonal influenza vaccine. Sanofi Pasteur has decades of experience producing seasonal influenza vaccines, which typically require annual strain changes, and which have been administered to hundreds of millions of people. In addition, the A (H1N1) vaccine manufactured by Sanofi Pasteur is produced by the same manufacturing process, and in the same facilities, that are used for producing the seasonal influenza vaccine.

Clinical trials conducted by Sanofi Pasteur as well as trials conducted by the National Institutes of Health have demonstrated that the A (H1N1) vaccine is similar to seasonal influenza vaccine both in terms of immunogenicity as well as safety. The Sanofi Pasteur trials confirm that one dose of *Influenza A (H1N1) 2009 Monovalent Vaccine* induces a robust antibody response in adults – but two doses of vaccine are needed to assure a robust antibody response in children nine years of age and younger. The two-dose regimen for these younger children is similar to the recommendations for seasonal influenza immunization in this age group.

The randomized, placebo-controlled, multicenter trials were conducted by Sanofi Pasteur to determine the immunogenicity and safety of the vaccine, given in two doses, with the second dose administered 21 days following the first dose. Immunogenicity was measured at day 21, just prior to administration of the second dose, and again at day 42.

No serious vaccine-related adverse events were reported during the 42 days of follow-up. Adverse event monitoring will continue for six months after administration of the second vaccine dose. Reported systemic reactions included mild fever, headache and fatigue, and reported local reactions included redness, swelling and pain at the injection site. These were similar to reactions studies of seasonal trivalent inactivated influenza vaccine administered to persons in comparable age groups.

The adult trial was conducted in 849 individuals divided into two age cohorts: 18 through 64 years of age; and 65 years of age and older. Study participants in each age cohort
were randomized to four treatment groups. Three groups received a 0.5 mL injection of non-adjuvanted vaccine formulated to contain 7.5, 15, or 30 mcg of hemagglutinin (HA) antigen. The fourth group received a placebo control (ClinicalTrials.gov registration number NCT00953524).

In the pediatric trial, 474 children were enrolled in two age cohorts: 6 months through 35 months of age; and 3 years through 9 years of age. The trial evaluated two vaccine formulations, 7.5 mcg and 15 mcg of HA antigen in each of two cohorts, with a third group receiving a placebo (ClinicalTrials.gov registration number NCT00952419).

At Day 42, 21 days following a second 7.5 mcg dose of Influenza A (H1N1) 2009 Monovalent Vaccine, seroprotection (defined as an antibody titer of 1:40 or greater) was achieved in 92 percent of children 6 months through 35 months of age; and following a second 15 mcg dose of the vaccine, seroprotection was achieved in 99 percent of children 3 through 9 years of age, 99 percent of adults 18 through 64 years of age, and in 95 percent of adults age 65 and older.

Sanofi Pasteur previously reported interim data showing that an immune response considered seroprotective was achieved following one 15 mcg dose of the vaccine in 50 percent of children 6 months through 35 months of age, 76 percent of children 3 through 9 years of age, 98 percent of adults 18 through 64 years of age, and 92 percent of adults age 65 and older.

### A Global Commitment

Sanofi Pasteur supports equitable allocation and access to vaccines – and has a deeply rooted history of contributing to the immunization needs of the developing world. As part of its worldwide contribution to public health, Sanofi Pasteur has committed to donating 100 million doses of influenza vaccine to the World Health Organization, to be delivered to the poorest countries to help combat a pandemic.

### The Importance of Vaccination

Influenza is a serious, potentially deadly disease – and the emergence of the new A (H1N1) virus is a reminder of the unpredictable nature of influenza – and the importance of prevention. Influenza activity related to the A (H1N1) virus continues to increase in the United States. For the week ending November 6, 2009, the Centers for Disease Control and Prevention (CDC) had reported widespread influenza activity in 48 states and said almost all of the influenza viruses identified so far this year continue to be 2009 H1N1 influenza A viruses.

Influenza-related hospitalizations and deaths are also increasing, and are higher than expected. Since April 2009, CDC has received reports of 129 laboratory-confirmed pediatric 2009 A (H1N1) deaths and another 15 pediatric deaths that were laboratory confirmed as influenza, but where the flu virus subtype was not determined.
The Threat of Seasonal Influenza

While the novel H1N1 influenza virus has been the focus of recent attention, it is important not to forget the risks posed by seasonal influenza viruses. On average each year, one out of five Americans suffers from seasonal influenza, approximately 226,000 are hospitalized, and 36,000 die from seasonal influenza and its complications.

Globally, seasonal influenza causes between three and five million cases of severe illness and 250,000 to 500,000 deaths every year.

For this reason, Sanofi Pasteur has worked closely with health authorities to determine the best balance of producing A (H1N1) and seasonal influenza vaccine. Given that seasonal influenza typically peaks in the U.S. in January or February, there is still plenty of time to be immunized before the anticipated peak transmission period.

Remember: the single best way to help prevent influenza is through annual vaccination.

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