



Testimony
Before the Subcommittee on Oversight and
Investigations
Committee on Energy and Commerce
United States House of Representatives

**Annual Influenza and Pandemic
Influenza Preparedness**

Statement of

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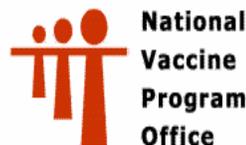
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For Release on Delivery
Expected at 2:00 PM
Wednesday, May 4, 2005

Chairman and members of the Committee, I am Dr. Bruce Gellin and I am the Director of the National Vaccine Program Office of the Department of Health and Human Services. I am pleased to appear before you today to discuss the U.S. influenza vaccination program and the role of the National Vaccine Program Office (NVPO) in strengthening U.S. influenza vaccine supply.

The National Vaccine Program Office was established in 1988 to improve prevention of disease through vaccination and to improve prevention of vaccine associated adverse events. NVPO has responsibility for coordinating and ensuring collaboration among the many federal agencies involved in vaccine and immunization activities. We have addressed this mission by communicating and coordinating with HHS' agencies, the Department of Defense and the US Agency for International Development, and through the National Vaccine Advisory Committee.

NVPO's mission is to:

- Coordinate and integrate activities of all Federal agencies involved in immunization efforts;
- Ensure that these agencies collaborate, so that immunization activities are carried out in an efficient, consistent, and timely manner;
- Develop and implement strategies for achieving the highest possible level of prevention of human diseases through immunization and the highest possible level of prevention of adverse reactions to vaccines; and

- Ensure that minimal gaps occur in Federal planning of vaccine and immunization activities.

The development, production and delivery of influenza vaccine every year underscores the complexities of vaccine production. Because they involve living organisms, developing and producing vaccines poses different challenges than drugs. In the United States, the protection of the population through vaccination depends on vaccines produced by private companies for profit as well as for public good.

U.S. Vaccine manufacturers are faced with substantial challenges including the costs and uncertainties in developing new products, limited returns on investment for vaccines compared with other pharmaceutical products, a regulatory environment that has high standards for safety and effectiveness, concerns about liability issues, and variable demand from one influenza season to the next. Consequently, the number of companies that produce licensed vaccines for the U.S. market is small and each type of vaccine is made by a limited number of suppliers. In many cases vaccines that we rely on in the U.S. are supplied by a single manufacturer.

Producing influenza vaccine has additional challenges. It is a vaccine that has to be redesigned and produced each year and delivered on-time to provide protection to tens of millions of people over a several month period in the fall in

advance of the annual influenza season. The fragility of this system was clearly documented during the past influenza season, when one of the two large influenza vaccine manufacturers could not supply vaccine to the U.S. market. Recent years also have seen surges in demand and delays in the delivery of influenza vaccine creating mismatches between vaccine availability and enhanced demand resulting in *de facto* shortages.

While we are optimistic that an increased number of manufacturers are interested in the U.S. influenza vaccine market by, presently only three companies are licensed to sell influenza vaccine in the U.S.; two produce inactivated influenza vaccine while the third produces a live-attenuated vaccine that is delivered by nasal spray. All U.S. licensed influenza vaccines are developed from viruses that are grown in embryonated eggs in a process unique for influenza vaccine. Because of the tight time lines to produce influenza vaccine, the influenza vaccine manufacturers begin production of the following season's vaccine even before the FDA's Vaccine and Related Biological Products Advisory Committee meets in mid-February to review global influenza surveillance data and officially select the components – the virus strains -- that are projected to be the predominant strains circulating in the U.S. during the following season. Both CDC and FDA contribute to influenza vaccine manufacturing by providing vaccine companies with vaccine reference strains -- so-called "seed viruses" -- as the starting point for large scale manufacturing. In a rotating fashion, each of the three vaccine virus strains selected for the

following year's vaccine composition are adapted to grow in eggs and are injected separately into millions of fertilized eggs, which are subsequently incubated to allow the influenza virus to grow. These egg-grown viruses are subsequently inactivated, purified, tested for potency, blended into the trivalent vaccine, and filled into syringes or vials. The number of influenza vaccine doses produced is limited by the capacity of the production facilities, the availability of embryonated eggs, the yield of influenza virus from each egg, and the length of time that manufacturing continues. Companies need to plan the amount of vaccine they will produce well in advance of the influenza season so that they can secure the needed egg supply in which vaccine viruses are grown.

Production of annual influenza vaccines, which contain three different influenza viruses, takes about six to nine months. Any disruption of the production schedule may lead to a delay in vaccine availability. Annual variation in the timing and severity of influenza outbreaks has resulted in significant fluctuations in demand for vaccine so that in some years supply is tight while in others, millions of vaccine doses go unused. Although it is possible for production to continue beyond the summer and into the fall, there is a substantial risk that late-season vaccine will go unused since the later vaccine is produced; the later it will be available to the clinics. Traditionally there has been little interest in "late season" vaccination – which in the United States is around Thanksgiving.

Thus, the current fragility in influenza vaccine supply largely is related to:

- A limited number of U.S.-licensed manufacturers

- Uncertainty regarding annual demand and the ability to sell all vaccine produced
- An inability to stockpile trivalent vaccine for longer than a year due to annual changes in the influenza viruses that circulate and cause disease such that vaccine not used in one season is generally not useful the following year
- A solely egg-based production system that has limited flexibility and surge capacity
- Financial and other barriers, to development and U.S. licensure of new influenza vaccines, and
- Limited interest by most of the public and health care community in providing “late season” vaccination

The limitations and disruptions of influenza vaccine supply also must be put within the context of continued high rates of mortality and morbidity each year from influenza disease and the need to improve our prevention program. In 2004, Acting Assistant Secretary for Health, Dr. Beato, asked the National Vaccine Advisory Committee (NVAC) to assess the influenza prevention program and to make recommendations on how this program could be improved. NVAC recommendations to strengthen influenza disease prevention included:

- Improving our understanding of influenza vaccine demand – and why so many of those for whom annual influenza vaccine is recommended do not get vaccinated (e.g., persons > 65 years of age, pregnant women and even health care workers),

- Reviewing the evidence that would support further expansion of the groups recommended for annual vaccination;
- Implementing systems to better track the burden of influenza illness and the effectiveness of the vaccination program; and,
- Conducting a thorough review of the Department's influenza research program to identify gaps, and strengthening of cross-Department collaboration.

A sufficient and secure influenza vaccine supply is a prerequisite if we are to implement these recommendations and improve influenza disease prevention by increasing vaccination coverage and expanding groups recommended for vaccination.

Influenza vaccine supply issues also are critical for pandemic influenza preparedness since the pandemic vaccine supply is directly related to existing influenza vaccine manufacturing capacity. Many experts believe that the risk of an influenza pandemic – or global epidemic – is higher than it has ever been in the past because of the spread of avian H5N1 influenza in multiple wild and domestic bird species across much of Asia. Since January 2004, 88 people, mostly young and otherwise healthy, have been confirmed by the World Health Organization to have been infected with the H5N1 influenza virus, and nearly two out of three of people who are known to have been infected have died as a result of this infection. Should this virus develop the capacity to be easily transmitted

among humans, either through a mutation or by mixing genes with a human influenza virus, a pandemic could result. Because H5 influenza viruses have not previously spread among people, the entire global population would be susceptible

We are all keeping a watchful eye on the current situation in Asia while at the same time recognizing that, in recent years, there also have been outbreaks of avian influenza infections and sporadic human cases caused by other influenza virus subtypes originating in Europe and in Canada as well as in Asia. A pandemic can unpredictably occur, could be caused by an influenza subtype other than H5, and could originate in any country.

Ensuring the ability to meet current annual demand for influenza vaccine, to improve the prevention of influenza disease, and to prepare for an influenza pandemic all require strengthening the influenza vaccine supply in the U.S. Building on the response to the influenza vaccine shortage in the 2004-05 season, NIH and FDA have worked to facilitate the clinical evaluation of an influenza vaccine produced by GSK and to expeditiously consider a licensure application such that this influenza vaccine may potentially be licensed for the upcoming season.

Several additional HHS influenza vaccine supply initiatives have been put in place to address pandemic preparedness needs and will also help to achieve

annual influenza prevention goals. The objectives of these initiatives are to secure and expand U.S. influenza vaccine supply, diversify production methods, and establish emergency surge capacity. To support these activities, HHS received \$50 million in FY2004 and \$99 million in FY2005. The President's Budget for FY2006 includes an additional \$120 million to further strengthen this component of the overall pandemic influenza preparedness efforts.

Because influenza vaccine is produced to meet the seasonal demand in the fall, production also is seasonal and embryonated eggs have not been available to manufacturers year-round. To enhance our Nation's ability to produce influenza vaccine at any time during the year, HHS issued a five-year contract to Sanofi-Pasteur of Swiftwater, Pennsylvania, on September 30, 2004 for \$40.1 million. Under this contract, Sanofi-Pasteur has already begun to change its flock management strategy to provide a secure, year-round supply of eggs suitable for influenza vaccine production at full manufacturing capacity. It also will increase the number of egg-laying flocks by 25% to provide contingency flocks in case of an emergency. These eggs may be used to support additional production of annual influenza vaccine in the event of a vaccine shortage with the doses being delivered later in the fall.

Diversification of influenza vaccine production methods also will help strengthen the system. Cell culture technology is a well-established vaccine production method for other vaccines such as the inactivated poliovirus vaccine and two

companies have registered their cell-culture based influenza vaccine technology in Europe. This production technology does not require eggs as a substrate for growth of vaccine virus, thereby avoiding the vulnerabilities associated with an egg-based production system. It also may be more amenable to surge capacity production when influenza vaccine supply needs to be expanded rapidly such as at the time of a pandemic. Additionally, cell culture technology uses a closed system that dramatically reduces the possibility for contamination. Finally, the new cell-based influenza vaccines provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines.

Secretary Leavitt announced last month that the Department of Health and Human Services issued a five-year contract on March 31, 2005 to Sanofi-Pasteur for \$97.1 million to develop cell culture influenza vaccine technology and conduct clinical trials, with the goal of obtaining an FDA license for this vaccine. Under this advanced development contract, the company also has committed to develop a plan to manufacture this vaccine at a U.S.-based facility with a capacity to manufacture 300 million doses of monovalent pandemic vaccine over a one year period.

These important steps to strengthen our national influenza vaccine supply through assuring the egg-supply and diversifying and expanding production capacity will be followed this year by additional measures to increase influenza vaccine production capacity and expand the number of influenza vaccine doses made using that capacity. Supported by the pandemic influenza vaccine initiative

in the FY'06 budget request for \$120 M, we posted synopses of three additional areas where we believe strategic investments move us toward achieving annual and pandemic influenza vaccine supply goals in the March 17, 2005 edition of FedBizOpps. On April 29, 2005, the first of these requests for proposals was posted, providing support for the development of cell-culture based and recombinant pandemic influenza vaccines. This contract, which we hope will lead to the licensure and U.S. production of a next generation influenza vaccine, will further increase production capacity and diversification of the manufacturing base.

Whereas building new influenza vaccine production facilities is an intermediate approach to expand the influenza vaccine supply, other strategies are more short term and expand the current vaccine capacity by increasing the efficiency with which influenza vaccine doses are produced. Influenza vaccine is manufactured in a series of steps – developing an influenza virus master seed for vaccine production, inoculating the virus into eggs, growing, harvesting, purifying, splitting, formulating, and filling it into vials or syringes. Improving efficiency at any step in this process can increase the eventual yield and number of vaccine doses produced. A second RFP will be issued this spring and will support improvements of the manufacturing process to increase overall influenza vaccine production at current manufacturing facilities.

The third RFP that will be issued is to provide support for research and development, leading to licensure of strategies that will stretch the number of

vaccine doses produced by decreasing the amount of influenza virus antigen that is needed in each dose. The concept underlying these “dose-stretching” strategies is that by changing either the influenza vaccine or the way it’s administered, you may be able to improve the immune response to vaccination and provide protection while using less of the vaccine antigen. By using less antigen in each vaccine dose, the number of doses that can be made at any level of production capacity would be significantly increased. The two most promising antigen-sparing approaches are either to add an adjuvant – a substance that stimulates the immune response to a vaccine formulation, or administering the vaccine into the skin (similar to the approach used in a skin test for Tb) where large numbers of immune cells are located. Both strategies have been evaluated in clinical trials and have the potential to expand influenza vaccine supply several-fold.

The increases in the FY 2006 President’s Budget request will support ongoing activities to ensure that the Nation will have an adequate influenza vaccine supply to respond better to yearly epidemics and to influenza pandemics. While issuing the requests for proposals and completing the contracts is only the first step toward the development of an expanded, diversified, and strengthened influenza vaccine supply, the U.S. is leading the global effort to develop vaccines and vaccine technologies to meet this challenge.

Thank you for your attention to my remarks this morning – and more importantly to the attention that you have paid to the prevention and control of annual and pandemic influenza.

I would be happy to answer any questions from the Committee.