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Pandemic Influenza: The Road to Preparedness

Statement of

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Mr. Chairman and members of the Committee, thank you for the opportunity to discuss with you the current global outbreak of avian influenza in fowl, the threat of pandemic influenza in humans, and the activities of the Federal Government in preparing to meet this threat.

An influenza virus strain capable of causing the next human influenza pandemic could emerge with little or no warning in almost any part of the world. Three influenza pandemics occurred in the 20th century, in 1918, 1957, and 1968. The pandemics of 1957 and 1968 were serious infectious disease events that killed approximately two million and 700,000 people worldwide, respectively. The 1918-1919 pandemic, however, was catastrophic: it killed more than 500,000 people in the United States and more than 40 million people worldwide. The possibility that a new influenza virus could emerge to cause a similar pandemic among human beings is a very real threat for which we must be prepared.

Of known influenza viruses, the H5N1 avian influenza strains that are spreading in domestic and migratory fowl in Asia and possibly Eastern Europe currently are of greatest concern. Although the H5N1 virus is primarily an animal disease, has not yet demonstrated the ability to spread efficiently from animals to humans and is very inefficient in spreading person-to-person, it has infected more than 120 people in Asia. Approximately half of the people diagnosed with H5N1 avian influenza infection have died. Because the virus is now endemic in many wild bird species in several countries in Asia, and likely elsewhere, eradication is probably not feasible. The feared human pandemic could become a reality if the H5N1 virus mutates further, remains highly virulent, and acquires the capability to spread as efficiently from person to person as do the commonly circulating virus strains that produce seasonal influenza epidemics. Even if H5N1 does not evolve into a pandemic strain, the possibility that a human influenza pandemic will occur at some time in the future is real.

On November 1, 2005, the President announced the *National Strategy for Pandemic Influenza*, and the next day U.S. Department of Health and Human Services (HHS) Secretary Michael O. Leavitt released an integral component of the *National Strategy*, the *HHS Pandemic Influenza Preparedness and Response Plan*. Together, these two documents provide a blueprint for a coordinated national strategy to prepare for and respond to a human influenza pandemic. The National Institutes of Health within HHS, and the HHS/NIH National Institute of Allergy and Infectious Diseases (NIAID), in particular, have the primary responsibilities for conducting scientific research and conducting clinical trials to foster product development to prepare our Nation for a potential human influenza pandemic.

In my testimony today, I will tell you more about the scientific research and development efforts of the Federal Government, the academic community, and the private sector to counter the threat of pandemic influenza. In particular, I will focus on projects and programs that will help ensure that effective influenza vaccines and antiviral drugs will be available to counter any human influenza virus with pandemic potential that could emerge.

Basic Science and Surveillance

HHS/NIH/NIAID supports numerous basic research projects intended to increase our understanding of how animal and human influenza viruses replicate, interact with their hosts, stimulate the immune response, and evolve into new strains. These studies lay the foundation for the design of new antiviral drugs, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike.

Each year, as influenza viruses circulate through the human population, their surface proteins undergo small changes. As these small changes accumulate, the influenza virus gains the ability to circumvent immunity created by prior exposure to older circulating influenza viruses or by vaccination.

This phenomenon, called “antigenic drift,” is the basis for the well-recognized patterns of human influenza disease that occur predictably every year, and is the reason, with the help of the World Health Organization (WHO), we must update influenza vaccines each year. Influenza viruses also can change more dramatically. For example, viruses can emerge that can jump species from natural reservoirs, such as wild ducks, to infect domestic poultry, farm animals, or humans. When an influenza virus jumps species from an animal, such as a chicken, to infect a human, the result is usually a “dead-end” infection that cannot readily spread further in the human population. However, mutations in the virus could develop that allow human-to-human transmission. Furthermore, if an avian influenza virus and another human influenza virus were to simultaneously co-infect a person or animal, the two viruses might swap genes, which could result in a virus that is readily transmissible between humans, and against which the population would have no natural immunity. These types of significant changes in influenza viruses are referred to as “antigenic shift.”

H5N1 and H9N2 are two avian influenza strains that have jumped directly from birds to humans, and which have significant pandemic potential. In 1998, 1999 and 2003, H9N2 influenza caused illness in three people in Hong Kong and in five individuals elsewhere in China, but the virus did not spread further among humans, and, reportedly, caused no deaths. At this time, H5N1 influenza appears to be a significantly greater threat than H9N2. In addition to the high fatality rate seen in people with H5N1 influenza, H5N1 viruses are evolving in ways that increasingly favor the start of a pandemic, including becoming more stable in the environment and expanding their host-species range. Moreover, two highly probable cases of human-to-human transmission of the H5N1 virus have occurred, and it is possible that other such transmissions have occurred.

An understanding of the diversity of influenza viruses—in the wild, in domestic animals, and in humans—as well as close surveillance for the emergence of new strains are important components of the scientific program to prepare for a

pandemic. HHS/NIH/NIAID supports major research programs that are important in this regard. One is a long-standing program based in Hong Kong to detect the emergence of influenza viruses with pandemic potential. Dr. Robert Webster and his team from St. Jude Children's Research Hospital conduct extensive surveillance of influenza viruses in animals in Asia, analyze new influenza viruses when they are found, and generate candidate vaccines against them. Another effort, the Influenza Genome Sequencing Project is a collaborative project of HHS/NIH (NIAID, the Institute for Genomic Research and the National Library of Medicine), the Wadsworth Center, the U.S. Department of Defense Armed Forces Institute of Pathology, St. Jude Children's Research Hospital, and several other organizations. Its purpose is to rapidly provide complete genetic sequences of thousands of influenza virus isolates to the scientific community. This program has enabled scientists to better understand how influenza viruses evolve as they spread through the population, and to match viral genetic characteristics with virulence, ease of transmissibility, and other clinical properties. A high priority of HHS is to further enhance international and domestic influenza surveillance systems so they can reliably detect an outbreak and to determine accurately the lethality and transmissibility of influenza strains.

Vaccines

Vaccines are an essential tool for the control of influenza. Unfortunately, current domestic capacity for the manufacturing of influenza vaccine can meet only a small fraction of the need projected for a pandemic response. For this reason, $4.7 billion of the $6.7 billion in the President's Fiscal Year (FY) 2006 supplemental appropriations request for the implementation of the *HHS Pandemic Influenza Plan* is intended to increase U.S.-based pandemic influenza vaccine-production capacity, vaccine stockpiles, and vaccine research. The goal is to have the capacity to produce sufficient pandemic influenza vaccine to protect every American within six months of an outbreak.

With regard to the development of an H5N1 vaccine, we have made rapid progress. HHS/NIH/NIAID-supported researchers at St. Jude Children's Research Hospital obtained a clinical isolate of a highly virulent H5N1 virus in Viet Nam in early 2004, and used a technique called reverse genetics to create an H5N1 vaccine reference strain from this isolate. HHS/NIH/NIAID then contracted with Sanofi-Pasteur and Chiron Corporation to manufacture pilot lots of 8,000 and 10,000 vaccine doses, respectively, of the inactivated virus vaccine, for use in clinical trials. The Sanofi Pasteur vaccine is now undergoing clinical testing in healthy adults and healthy elderly people, and will soon begin evaluation in children.

Preliminary results from these trials provide both good and sobering news. The good news is that the vaccine is safe, and induces a vigorous immune response that augurs well for protecting people against the H5N1 virus. The sobering news is that two large doses of the Sanofi product were needed to elicit an immune response likely to be protective. However, preliminary results from a Phase I clinical trial of an H9N2 influenza vaccine candidate made by Chiron indicate that addition of an adjuvant—a vaccine component that increases the immune response—can reduce the required dose substantially. Clinical trials of H5N1 candidates using adjuvants and other strategies to reduce the necessary dose are ongoing or imminent.

In addition to these inactivated virus vaccines, HHS/NIH/NIAID is collaborating with industry to pursue several other vaccine strategies. These include recombinant subunit vaccines, in which cultured cells are genetically engineered to produce influenza virus proteins that are then used in a vaccine, and DNA vaccines, in which scientists inject influenza genetic sequences directly into the vaccinee to stimulate an immune response. In addition, from the mid-1970s to the early 1990s, HHS/NIH/NIAID intramural and extramural researchers developed a cold-adapted, live attenuated influenza vaccine strain that later became the influenza vaccine marketed as FluMist®, licensed by the HHS Food

and Drug Administration (FDA),. Today, HHS/NIH/NIAID intramural researchers are working with colleagues from MedImmune, Inc., under a Cooperative Research and Development Agreement to produce and test a library of similar vaccine candidates against all known influenza strains with pandemic potential.

HHS also has awarded over $162 million in contracts to Sanofi-Pasteur and Chiron to produce bulk inactivated H5N1 vaccine for the Strategic National Stockpile to ensure the manufacturing techniques, procedures, and conditions used for large-scale production will yield a satisfactory product. Moving to large-scale production of the vaccine in parallel with clinical testing of pilot lots is an indication of the urgency with which we have determined we must address H5N1 vaccine development. We could use the doses of H5N1 vaccine we have ordered, as necessary, to vaccinate health care workers, researchers, and, if indicated, the public in affected areas.

In addition to creating a safe and effective vaccine candidate, it is imperative we have the ability to produce large quantities of vaccine quickly, in the United States. To accomplish this, HHS is pursuing a multi-faceted strategy to create domestic influenza vaccine manufacturing capacity capable of producing 300 million vaccine courses within six months of the onset of a human influenza pandemic.

The initial component of this strategy is to increase the number of domestic manufacturers of traditional egg-based influenza vaccines; only one currently exists within the United States. Doing so will allow the United States to manufacture a 20 million course pre-pandemic vaccine stockpile by 2009, without disrupting the production of annual seasonal influenza vaccine. In the event a pandemic appears imminent—or earlier if circumstances warrant— we could use this pre-pandemic vaccine to immunize healthcare workers, front-line responders, vaccine-manufacturing personnel, and others critical to the pandemic response. With the addition of the domestic infrastructure required to

produce the pre-pandemic vaccine, egg-based production capacity will be able to provide an additional 60 million courses of vaccine within six months of the emergence of a pandemic.

Egg-based production alone, however, cannot bring us to our goal of having the surge capacity in the United States to produce 300 million courses of vaccine in a six-month time frame. Instead, the best hope for acquiring a vaccine manufacturing capacity in the United States we could to ramp up rapidly on short notice lies in expanding and accelerating our investment in non-egg-based technologies, specifically cell-based influenza vaccines. Much of the investment in vaccines outlined in the HHS *Plan* goes toward this initiative. The proposed investments will allow creation of new domestic facilities that would provide the surge capacity to manufacture approximately 240 million vaccine courses within six months of a pandemic outbreak.

The HHS *Plan* also calls for upgrading existing domestic manufacturing facilities to enable the production of pandemic influenza vaccine in an emergency. To that end, HHS will work with HHS/FDA to establish contingency arrangements with vaccine manufacturers that will allow them to quickly adapt their facilities either to produce influenza vaccines or to carry out other critical functions, such as repackaging bulk vaccine produced by other manufacturers.

It is important to note, however, that while the technology for producing influenza vaccine in cell cultures is promising, successful development of the production methods and licensure of the product are years in the future, and by no means guaranteed. Moreover, how quickly we reach our production goals will depend on the development of adjuvants and other dose-sparing techniques that could reduce the amount of vaccine needed to protect the U.S. population, and on whether required incentives for industry can be successfully implemented.

Recognizing the urgent need to create and expand vaccine-manufacturing capacity, we must remove or mitigate deterrents to participation in the vaccine enterprise by companies with substantial industrial capacity and experience. Accordingly, the Administration is proposing limited liability protections for vaccine manufacturers and providers, except in cases of willful misconduct. We believe this proposal will reduce the liability risks that dissuade companies from producing pandemic countermeasures, while retaining appropriate access by the American public to reasonable and justified court remedies.

Under the International Partnership on Avian and Pandemic Influenza the President launched in September, we are also beginning to coordinate our vaccine research with that undertaken by other nations and the private sector outside the United States. The World Health Organization Secretariat this week sponsored the first of what we hope will be a series of meetings to allow us to exchange information with and learn from our colleagues in other countries who are in various stages of research on human vaccines against the H5N1 virus. HHS/NIHNIAID and the Office if Public Health Emergency Preparedness are also providing technical assistance to the Government of Viet Nam as it proceeds with the development of a human H5N1 vaccine, including support for clinical trials.

Antivirals

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to prevent illness after exposure and to treat infection after it occurs. Four drugs currently are available for the treatment of influenza, three of which HHS/FDA has also licensed for influenza prevention for certain populations. HHS/NIH/NIAID supports research to identify new anti-influenza drugs through the screening of new drug candidates in cell-culture systems and in animal models. In the past year, we have identified seven promising candidates. Efforts to design drugs that precisely target viral proteins and inhibit their functions also are under way. In addition, HHS/NIH/NIAID is developing novel, broad-spectrum therapeutics that might work against many influenza virus strains. Some of these target viral entry into human cells, while others specifically attack and degrade the viral genome.

Efforts also are under way to test and improve the existing anti-influenza drugs Researchers have determined that currently circulating H5N1 viruses are resistant to two older drugs—rimantadine and amantadine—but are sensitive to a newer class of drugs, called neuraminidase inhibitors. This class of drugs includes oseltamivir (marketed as Tamiflu®), approved by HHS/FDA for treatment of individuals older than one year. Studies to further characterize the safety profile of oseltamivir for very young children are in the advanced planning stage. Studies are also in progress to evaluate novel drug targets, as well as long-acting next-generation neuraminidase inhibitors. In addition, development and testing in animals of a combination antiviral regimen against H5N1 and other potential pandemic influenza strains are under way.

If a human influenza pandemic were to occur, a sufficient supply of stockpiled antiviral drugs to treat and care for infected individuals would be critical. Therefore, the HHS *Plan* requests an investment of $1.4 billion to increase the availability of these drugs. These funds would help us achieve the President's goal of having available 81 million courses of antivirals, which would be sufficient

to treat 25 percent of the U.S. population (75 million courses) and also allow for a reserve supply (6 million courses) we could use to contain an initial U.S. outbreak. Funding would also accelerate the development of promising new antiviral drug candidates in collaboration with academia and industry, since there is a possibility that none of the antivirals available today will be fully effective against whatever strain sparks a pandemic influenza among humans.

The planned acquisition by the U.S. Government of up to 81 million courses of antiviral drugs will enable manufacturers to make significant expansion in U.S.-based manufacturing capacity, and thereby position the United States to meet future demands much more readily than is currently possible. HHS also will work with its State partners to encourage them to acquire antivirals for rapid use for their populations.

Conclusion

In closing, Mr. Chairman, I want to reiterate that the threat from pandemic influenza, whether from an H5N1 influenza virus or another influenza virus still unknown, is real and growing. Along with Under Secretary Dobriansky and Dr. Gerberding, I participated in the trip that Secretary Leavitt led to Southeast Asia last month, and what I saw confirmed this belief. Although we do not know when the next human influenza pandemic will occur, or how devastating it will be, we can be certain that a new influenza virus ultimately will emerge. And the historical precedent of the 1918 pandemic clearly demonstrates that a newly emerging influenza virus can wreak catastrophic damage worldwide in a matter of months.

The world is obviously very different today than it was in 1918. In some ways we are more vulnerable. Travel that took weeks in 1918 only takes hours today. Our globalized economy is exquisitely sensitive to the disruptions that would inevitably occur during a pandemic. Many parts of the world have weak public health and health-care delivery systems, and poverty and overcrowding are

widespread, as we witnessed in Southeast Asia. Science and medicine, though, have progressed dramatically, and we now have tools such as sophisticated viral surveillance techniques, effective vaccines, antibiotics to treat secondary bacterial infections, and antiviral drugs against influenza that should aid in our response to an emerging influenza pandemic. These tools, however, will be of little use if we cannot bring them to bear when we need them. For that to occur, we must take all possible measures now to ensure that our public health and pharmaceutical manufacturing infrastructure is equipped to respond to a pandemic.

Thank you for this opportunity to testify before you today. I would be pleased to answer any questions that you may have.