But, more importantly, the next step is trying to think about the kinds of capacity and the kinds of production technologies that may improve where we are. Eggs have served us well, but they have some limitations, and we have put significant funds to try to accelerate the development of new technologies that can allow what we described as surge capacity and more vaccine to be produced.

And, finally, to that point, in addition to developing these vaccines, accelerating the development, getting them licensed, part of the criteria to this funding stream is to develop facilities so that ultimately these new vaccines will be produced in the United States.

Ms. Watson. OK, I am sorry, I am out of time. I was just going to join with my friend, Congressman Dan Burton, on the mercury issue and the slow movement that has taken place slowly in trying to improve.

So there are other questions, too, but I know I am out of time, Mr. Chairman.

Mr. Shays. Thank you.

Ms. Watson. Thank you for the time.

Mr. Shays. We have another that is a rather large panel, so we will get to that and just thank all of our witnesses. We will be following up with some questions. Mr. Burton may have some; I know the committee does. Ambassador Watson may as well, and the ranking member and others may. So thank you all very much.

We will announce our second panel. It is Dr. Crosse, Director of Health Care Issues, U.S. Government Accountability Office; Ms. Selecky, Washington State Secretary of Health, testifying on behalf of the Association of State and Territorial Health Officials; Dr. Hearne, executive director, Trust for America's Health; Dr. John Milligan, executive vice president and chief financial officer, Gilead Sciences, Inc.; and Mr. Abercrombie, president and chief executive officer, Hoffman-La Roche, Inc., accompanied by Dr. Dominick Iacuzio, medical director, Roche Laboratories.

We have enough seats for everyone there? Stay standing, if you would, because we are going to swear you in.

[Witnesses sworn.]

Mr. Shays. Note for the record our witnesses have responded in the affirmative.

And we will start with you, Dr. Crosse, and we will just go right up.

Dr. Crosse. Thank you.

Mr. Shays. Five minutes is the time allotted. Obviously, if you go over a minute or two, we can live with that. But we have a large panel and a busy schedule today. Thank you.

Dr. Crosse.
STATEMENTS OF DR. MARCIA CROSSE, DIRECTOR, HEALTH CARE ISSUES, U.S. GOVERNMENT ACCOUNTABILITY OFFICE; MARY C. SELECKY, WASHINGTON STATE SECRETARY OF HEALTH, TESTIFYING ON BEHALF OF THE ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICIALS; DR. SHELLEY A. HEARNE, EXECUTIVE DIRECTOR, TRUST FOR AMERICA'S HEALTH; DR. JOHN F. MILLIGAN, EXECUTIVE VICE PRESIDENT AND CHIEF FINANCIAL OFFICER, GILEAD SCIENCES, INC.; AND GEORGE B. ABERCROMBIE, PRESIDENT AND CHIEF EXECUTIVE OFFICER, HOFFMAN-LA ROCHE, INC., ACCOMPANIED BY DR. DOMINICK IACUZIO, MEDICAL DIRECTOR, ROCHE LABORATORIES, INC.

STATEMENT OF DR. MARCIA CROSSE

Dr. CROSSE. Thank you. I am pleased to be here today as you discuss issues regarding our preparedness to respond to an influenza pandemic. Shortages of influenza vaccine in the 2004–2005 influenza season, as well as mounting concern about avian influenza activity in Asia, have raised concerns about the Nation’s preparedness to deal with a pandemic.

As we have heard, given the global nature of disease, a pandemic that begins abroad could quickly spread to this country.

You asked us to provide our perspective on the Nation’s preparedness for responding to an influenza pandemic, including lessons learned from the previous influenza season, that would be applicable for pandemic preparedness.

Although an influenza pandemic will differ from a routine influenza season, experience during the 2004–2005 shortage illustrates the importance of developing a workable distribution plan, identifying priority groups in local populations, and developing plans for mass vaccinations in advance.

The Nation faces multiple challenges to prepare for and respond to an influenza pandemic. Key questions remain about the Federal role in purchasing and distributing vaccines during a pandemic. HHS’s current draft pandemic preparedness plan does not establish the actions the Federal Government would take to purchase or distribute vaccine during an influenza pandemic, and leaves it up to States to select among three options: public sector purchase of all pandemic influenza vaccine; a mixed public-private system, where public sector supply may be targeted to specific priority groups; or maintenance of the current, largely private, system.

However, if States are to purchase vaccine, they may need to undertake efforts in advance to establish the necessary funding sources, authority, or processes. For example, during this past winter, the State of Minnesota tried to sell some of its vaccine to other States that needed additional vaccine for their high-risk populations. But some States lacked the funding or authority under State law to purchase the vaccine when Minnesota offered it.

HHS’s draft pandemic plan indicates that, as information about virus severity becomes available, recommendations on priority groups for early vaccination will be developed at the national level. However, during the past vaccination season, in some places there was not enough vaccine to cover everyone in the priority groups, so States set their own priorities. Maine, for example, initially ex-
cluded healthcare workers because State officials estimated that there was not enough vaccine to cover everyone in the nationally designated groups.

In addition, clear communication will be a big challenge. State health officials reported this past winter that mixed messages created confusion. For example, when CDC advised those persons aged 65 and over to get vaccinated, and some States, including California, advised those persons aged 50 and over to get vaccinated.

Further, some individuals found themselves in a communication loop that provided no answers on where to be vaccinated. CDC advised people to contact their local public health department. However, some public health departments told callers to contact their physician. But when they called their physician, they were told to call their public health department. This lack of a reliable source of information led to confusion and much frustration.

Further challenges include ensuring an adequate and timely supply of influenza vaccine and antiviral drugs, which can help prevent or mitigate the number of influenza-related deaths. As we learned this past season, and as we have heard repeatedly today, the vaccine supply is fragile; it takes many months to produce vaccine; and problems with even a single manufacturer can result in vaccine shortages. Particularly given the length of time needed to produce vaccines, influenza vaccine may be unavailable, in short supply, or delayed, and might not be widely available during the initial stages of a pandemic.

Further, our current stockpile of antiviral drugs is insufficient to meet the likely demand in a pandemic. As was discussed earlier, HHS is working to expand vaccine production capacity and to stockpile vaccine and antiviral drugs, but it will be years before these preparations are in place.

Finally, the lack of sufficient hospital and healthcare work force capacity to respond to an infectious disease outbreak may also affect response efforts during an influenza pandemic. Public health officials we spoke with said that, at a minimum, a large-scale outbreak could strain the available capacity of hospitals by requiring entire hospital sections, along with their staff, to be used as isolation facilities.

In summary, important challenges remain in the Nation’s preparedness and response should an influenza pandemic occur in the United States. As we learned in the 2004–2005 influenza season, when vaccine supply is limited, planning and effective communication are critical to ensure timely delivery of vaccine to those who need it. HHS’s current draft plan lacks some key information for planning our Nation’s response to a pandemic.

It is important for the Federal Government and the State to work through critical issues, such as how vaccine will be purchased, distributed, and administered; which population groups are likely to have priority for vaccination; what communication strategies are most effective; and how to address issues related to vaccine and antiviral supply, and hospital and work force capacity before we are in a time of crisis.
Until key Federal decisions are made, public health officials at all levels may find it difficult to plan for an influenza pandemic, and the timeliness and adequacy of response efforts may be compromised.

Mr. Chairman, this concludes my prepared statement.

[The prepared statement of Dr. Crosse follows:]
INFLUENZA PANDEMIC
Challenges in Preparedness and Response

Statement of Marcia Crosse
Director, Health Care
INFLUENZA PANDEMIC

Challenges in Preparedness and Response

Why GAO Did This Study

Shortages of influenza vaccine in the 2004-05 and previous influenza seasons and mounting concern about recent avian influenza activity in Asia have raised concern about the nation’s preparedness to deal with a worldwide influenza epidemic or influenza pandemic. Although the extent of such a pandemic cannot be predicted, according to the Centers for Disease Control and Prevention (CDC), an agency within the Department of Health and Human Services (HHS), it has been estimated that in the absence of any control measures such as vaccination or antiviral drugs, a "moderate-level" influenza pandemic could kill up to 200,000 people in the United States, affect from 10 to 30 percent of the U.S. population, and generate associated costs ranging from $71 billion to $167 billion in the United States.

GAO was asked to discuss the challenges the nation faces in responding to the threat of an influenza pandemic, including the lessons learned from previous annual influenza seasons that can be applied to its preparedness and overall ability to respond to a pandemic. This testimony is based on GAO reports and testimony issued since 2000 on influenza vaccine supply, pandemic planning, emergency preparedness, and emerging infectious diseases and on current work examining the influenza vaccine shortage in the United States for the 2004-05 influenza season.

What GAO Found

The nation faces multiple challenges to prepare for and respond to an influenza pandemic. First, key questions about the federal role in purchasing and distributing vaccines during a pandemic remain, and clear guidance on potential priority groups is lacking in HHS’s current draft of its pandemic preparedness plan. For example, the draft plan does not establish the actions the federal government would take to purchase or distribute vaccine during an influenza pandemic. In addition, as was highlighted in the nation’s recent experience responding to the unexpected influenza vaccine shortage for the 2004-05 influenza season, clear communication of the nation’s response plan will be a major challenge. During the 2004-05 influenza season, state health officials reported that mixed messages created confusion. For example, CDC advised vaccination for persons aged 65 and older, and at the same time a state advised vaccination for persons aged 50 and older. Further challenges include ensuring an adequate and timely supply of influenza vaccine and antiviral drugs, which can help prevent or mitigate the number of influenza-related deaths. Particularly given the length of time needed to produce vaccines, influenza vaccine may be unavailable or in short supply and might not be widely available during the initial states of a pandemic. Finally, the lack of sufficient hospital and health care workforce capacity to respond to an infectious disease outbreak may also affect response efforts during an influenza pandemic. Public health officials we spoke with said that a large-scale outbreak, such as an influenza pandemic, could strain the available capacity of hospitals by requiring entire hospital sections, along with their staff, to be used as isolation facilities.
Mr. Chairman and Members of the Committee:

I am pleased to be here today as you discuss the nation’s preparedness to respond to a worldwide influenza epidemic—known as a pandemic. Shortages of influenza vaccine in the 2004–05 and previous annual influenza seasons, as well as mounting concern about recent avian influenza activity in Asia, have raised concern about the nation’s preparedness to deal with a pandemic. Pandemic influenza, which arises periodically but unpredictably from a major genetic change in the influenza virus, can lead to worldwide disease and death. Although the extent of the next pandemic cannot be predicted, modeling studies suggest that its effect in the United States could be severe. According to the Centers for Disease Control and Prevention (CDC), it has been estimated that in the absence of any control measures such as vaccination and drugs, a "medium-level'' influenza pandemic in the United States could kill 89,000 to 287,000 people, affect from 15 to 35 percent of the U.S. population, and generate associated costs ranging from $71 billion to $167 billion. In the event of a pandemic, the nation will likely experience a vaccine shortage. The nation’s experience responding to the unexpected shortage of annual influenza vaccine during the 2004–05 influenza season—in which public health officials sought to match available vaccine supply with demand—underscores the challenges that federal, state, and local entities would need to meet in the event of a pandemic. In addition, our recent work has highlighted other challenges in responding to pandemic influenza.

You asked us to provide our perspective on the nation’s preparedness for responding to an influenza pandemic, including the lessons learned from previous annual influenza seasons that would be applicable to pandemic preparedness. In this testimony, I will discuss challenges we identified related to (1) planning for the purchase and distribution of influenza vaccine, including defining priority groups to be vaccinated; (2) communicating information about the situation and the response plan clearly and effectively among health officials, providers, and the public;

1An influenza pandemic is defined by the emergence of a novel influenza virus, to which much or all of the population is susceptible, that is readily transmitted person to person, and causes outbreaks in multiple countries.

2Influenza pandemics can have successive "waves'' of disease and last for up to 3 years. Three pandemics occurred in the 20th century: the "Spanish influenza'' of 1918, which killed about 500,000 people in the United States; the "Asian influenza'' of 1957, which killed about 70,000 people in the United States; and the "Hong Kong influenza'' of 1968, which killed about 24,000 people in the United States.
ensuring an adequate supply of vaccine and antiviral drugs; and
addressing hospital and workforce capacity to respond to large-scale outbreaks of infectious disease, including pandemic influenza.

My testimony today is based on reports and testimony on influenza vaccine supply, pandemic planning, emergency preparedness, and emerging infectious diseases that we have issued since October 2007 and on a review in progress for this committee on actions taken and lessons learned at federal, state, and local levels to ensure that high-risk individuals had access to vaccine during the 2004-05 influenza vaccine shortage. Our prior work includes analysis of information provided by and interviews with officials in the Department of Health and Human Services (HHS), specifically from CDC, the Food and Drug Administration (FDA), and the National Vaccine Program Office. We also interviewed public health department officials, vaccine manufacturers, and vaccine distributors; surveyed physician group practices; and reviewed HHS's August 2004 draft Pandemic Influenza Preparedness and Response Plan. Since March 2005 we have reviewed documents and interviewed officials from HHS, CDC, and the National Vaccine Program Office, national organizations, including the Association of State and Territorial Health Officials; organizations that conduct mass immunization clinics; a major vaccine manufacturer; and a large purchaser of influenza vaccine. We also conducted site visits at a judgmental sample of states and localities. We conducted our work in accordance with generally accepted government auditing standards. CDC and the National Vaccine Program Office provided comments on the facts contained in this statement, and we made changes as appropriate.

In summary, the nation faces multiple challenges to prepare for and respond to an influenza pandemic. First, key questions remain about the federal role in purchasing and distributing vaccine during a pandemic; and clear guidance on potential priority groups is lacking in HHS's current draft of its pandemic preparedness plan. In addition, as highlighted by the nation's recent experience responding to the unexpected influenza vaccine

See "Related GAO Products" at the end of this testimony for a list of our earlier work related to infectious diseases, influenza vaccine supply, and pandemic planning.

The states included California, Florida, Maine, Minnesota, and Washington, and the localities included San Diego and San Francisco, California; Miami-Dade County, Florida; Portland, Maine; Seattle County, Minnesota; and Seattle-King County, Washington. We selected these states and localities on the basis of geography, population size, and state vaccination success rates.
shortage for the 2004–05 influenza season, clear communication of the nation’s response plan will be a major challenge. Further challenges include ensuring an adequate and timely supply of influenza vaccine and antiviral drugs, which can help prevent or mitigate the number of influenza-related deaths. Finally, the lack of sufficient hospital and health care workforce capacity to respond to an infectious disease outbreak may also affect response efforts during an influenza pandemic.

**Background**

Influenza is more severe than some other viral respiratory infections, such as the common cold. Most people who contract influenza recover completely in 1 to 2 weeks, but some develop serious and potentially life-threatening medical complications, such as pneumonia. People aged 65 and older, people of any age with chronic medical conditions, children younger than 2 years, and pregnant women are generally more likely than others to develop severe complications from influenza.

Vaccination is the primary method for preventing influenza and its more severe complications. Produced in a complex process that involves growing viruses in millions of fertilized chicken eggs, influenza vaccine is administered annually to provide protection against particular influenza strains expected to be prevalent that year. Experience has shown that vaccine production generally takes 6 or more months after a virus strain has been identified; vaccines for certain influenza strains have been difficult to mass-produce. After vaccination, it takes about 2 weeks for the body to produce the antibodies that protect against infection. According to CDC recommendations, the optimal time for vaccination is October through November, because the annual influenza season typically does not peak until January or February. Thus, in most years vaccination in December or later can still be beneficial.

At present, two vaccine types are recommended for protection against influenza in the United States: an inactivated virus vaccine injected into muscle and a live virus vaccine administered as a nasal spray. The injectable vaccine—which represents the large majority of influenza vaccine administered in this country—can be used to immunize healthy individuals and those at highest risk for complications, including those with chronic illness and those aged 65 and older, but the nasal spray vaccine is currently approved for use only among healthy individuals aged 6 to 49 years who are not pregnant. Vaccine manufacture and purchase
take place largely within the private sector; for the 2004-05 influenza season, two companies (one producing the injectable vaccine and one producing the nasal spray) manufactured vaccine for the U.S. market.4

Although vaccination is the primary strategy for protecting individuals who are at greatest risk of serious complications and death from influenza, antiviral drugs can also contribute to the treatment and prevention of influenza. Four antiviral drugs have been approved for treatment. If taken within 48 hours of symptoms beginning, these drugs can reduce symptoms and make someone with influenza less contagious to others. Three of the four antiviral drugs are also approved for prevention; according to CDC, they are about 70 to 90 percent effective for preventing illness in healthy adults.

HHS has primary responsibility for coordinating the nation’s response to public health emergencies. As part of its mission, the department has a role in the planning needed to prepare for and respond to an influenza pandemic. One action the department has taken is to develop a draft national pandemic influenza plan, titled Pandemic Influenza Preparedness and Response Plan, which was released in August 2004 for a 60-day comment period. Within HHS, CDC is the principal agency for protecting the nation’s health and safety. CDC’s activities include efforts to prevent and control diseases and to respond to public health emergencies. CDC and its Advisory Committee on Immunization Practices (ACIP) recommend which population groups should be targeted for vaccination each year and, when vaccine supply allows, recommends that any person who wishes to decrease his or her risk of influenza-like illness be vaccinated. FDA, another HHS agency, also plays a role in preparing for the annual influenza season and for a potential pandemic. FDA is responsible for ensuring that new vaccines and drugs are safe and effective. The agency also regulates and licenses vaccines and antiviral agents.5

HHS has limited authority to control vaccine production and distribution directly; influenza vaccine supply and marketing are largely in the hands of

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4HHS also licensed and purchased about 1.5 million doses of vaccine from manufacturers not licensed in the United States. Although this vaccine could be made available to be administered under special protocols, according to HHS officials, none of the vaccine was used in the 2004-05 influenza season.

5In addition, FDA develops influenza vaccine strains and regenerates and makes them available to manufacturers for vaccine development and evaluation.
the private sector. Although the Public Health Service Act authorizes the Secretary of HHS to “take such action as may be appropriate” to respond to a public health emergency, as determined and declared by the Secretary, it is not clear whether or to what extent the Secretary could directly influence the manufacture or distribution of influenza vaccine to respond to an influenza pandemic. The appropriateness of the Secretary’s response would depend on the nature of the public health emergency, for example on the available evidence relating to a pandemic. According to a senior HHS official involved in HHS emergency preparedness activities, manufacturers of vaccine for the U.S. market have agreed in principle to switch to production of pandemic influenza vaccine should the need arise and proper compensation and indemnification be provided; therefore, he said, it would probably be unnecessary for the federal government to nationalize vaccine production, although the federal government has the legal authority to do so if circumstances warrant it.

For the 2004-05 influenza season, CDC estimated as late as September 2004 that about 100 million doses of vaccine would be available for the U.S. market. CDC and ACIP recommended vaccination for about 185 million people, including roughly 86 million people at high risk for complications. On October 5, 2004, however, one manufacturer announced that it could not provide its expected production of 40-45 million doses—roughly half of the U.S. supply of expected vaccine.\(^3\)

\(^3\)Under the Federal Food, Drug, and Cosmetic Act, FDA ensures compliance with good manufacturing practice. FDA has limited authority to prohibit the sale of prescription drugs, including influenza vaccine, that have been purchased by health care entities such as public or private hospitals. The authority would not extend to resale of the vaccine for emergency medical reasons. The term “health care entity” does not include wholesale distributors.

3According to the act, to declare a public health emergency, the Secretary must determine that (1) a disease or disorder presents a public health emergency or (2) a public health emergency, including significant outbreaks of infectious disease or bioterrorist attacks, otherwise exists. Public Health Service Act § 314 (current version at 42 U.S.C. § 247d).


3The license for this manufacturer, with production facilities in Liverpool, England, was temporarily suspended by British regulatory authorities.
Because a large proportion of vaccine produced by the other major manufacturer of injectable vaccine had already been shipped before October 5, 2004, about 25 million doses of injectable vaccine for high-risk individuals and others, and about 1 million doses of the nasal spray vaccine for healthy people, were available after the announcement to be distributed to Americans who wanted an influenza vaccination.

Preparing for and responding to an influenza pandemic differ in several respects from preparing for and responding to a typical influenza season. For example, past influenza pandemics have affected healthy young adults who are not typically at high risk for complications associated with influenza, and a pandemic could result in an overwhelming burden of ill persons requiring hospitalization or outpatient medical care. In addition, the demand for vaccine may be greater in a pandemic.

Planning for Purchase and Distribution of Vaccine and Defining Priority Groups

Challenges remain in planning for purchase and distribution of vaccine and defining priority groups in the event of a pandemic. HHS has not finalized planning for an influenza pandemic, leaving unanswered questions about the nation’s ability to prepare for and respond to such an outbreak. For the past 5 years, we have been urging HHS to complete its pandemic influenza plan. The document remains in draft form, although federal officials said in June 2005 that an update of the plan is being completed and is expected to be available in summer 2005. Key questions about the federal role in purchasing and distributing vaccines during a pandemic remain, and clear guidance on potential groups that would likely have priority for vaccination is lacking in the current draft plan.

One challenge is that the draft pandemic plan does not establish the actions the federal government would take to purchase or distribute vaccine during an influenza pandemic. Rather, it describes options for vaccine purchase and distribution, which include public-sector purchase of all pandemic influenza vaccine; a mixed public-private system where public-sector supply may be targeted to specific priority groups; and maintenance of the current largely private system. The draft plan does not specifically recommend any of these options. According to the draft plan, the federal government’s role may change over the course of a pandemic, with greater federal involvement early, when vaccine is in short supply. Noting that several uncertainties make planning vaccination strategies difficult, the draft plan states that national, state, and local planning needs to address possible contingencies, so that appropriate strategies are in place for whichever situation arises.
If public-sector vaccine purchase is an option, establishing the funding sources, authority, or processes to do so quickly may be needed. During the 2004-05 shortage, some state health officials reported problems with states’ ability, with regard to both funding and the administrative process, to purchase influenza vaccine. For example, during the effort to redistribute vaccine to locations of greatest need, the state of Minnesota tried to sell its available vaccine to other states seeking additional vaccine for their high-risk populations. According to federal and state health officials, however, certain states lacked the funding or authority under state law to purchase the vaccine when Minnesota offered it. In response to problems encountered during the 2004-05 shortage, the Association of Immunization Managers proposed in 2005 that federal funds be set aside for emergency purchase of vaccine by public health agencies and that cost not be a barrier in acquiring vaccine to distribute to the public.\(^5\)

Although an influenza pandemic may differ from an annual influenza season, experience during the 2004-05 shortage illustrates the importance of having a distribution plan in place ahead of time to prevent delays when timing is critical:

- **Collaborating with stakeholders to create a workable distribution plan in time consuming.** After the October 5, 2004, announcement of the sharp reduction in influenza vaccine supply, CDC began working with the sole remaining manufacturer of injectable vaccine on plans to distribute the manufacturer’s remaining supply to providers across the country. The plan had two phases and benefited from voluntary compliance by the manufacturer to share proprietary information to help identify geographic areas of greatest need for vaccine. The first phase, which began in October 2004, filled or partially filled orders from certain provider types, including state and local public health departments and long-term care facilities. The second phase, which began in November 2004, used a formula to apportion the remaining doses across the states according to each state’s estimated percentage of the national unmet need. States could then allocate doses from their apportionment to providers and facilities, which would purchase the vaccine through a participating distributor. The state ordering process under the second phase continued through mid-January. Health officials in several states commented on the late availability of this vaccine; officials in one state, for example, remarked that the phase two vaccine was "too much, too late."

\(^5\)The Association of Immunization Managers is an organization that represents 64 state, territorial, and urban-area immunization programs funded by CDC.
• Identifying priority groups in local populations also takes time. Federal, state, and local officials need to have information on the population of the priority groups and the locations where they can be vaccinated to know how, where, and to whom to distribute vaccine in the event of an influenza pandemic. During the 2004-05 influenza season, federal officials developed a distribution plan to allocate a limited amount of vaccine, but the states also had to determine how much vaccine was needed and where to distribute it within their own borders. For example, state health officials in Florida did not know exactly how many high-risk individuals needed vaccination, so they surveyed long-term care facilities and private providers to estimate the amount of vaccine needed to cover high-risk populations. It took nearly a month for state officials to compile the results of the surveys, to decide how many doses needed to be distributed to local areas, and to receive and ship vaccine to the counties.

• Distributing the vaccine to a state or locality is not the same as administering the vaccine to an individual. Once vaccine has been distributed to a state or local agency, individuals living in those areas still need to be vaccinated. Vaccinating a large number of people is challenging, particularly when demand exceeds available supply. For example, during the 2004-05 influenza season, many places giving vaccinations right after the shortage was announced were overwhelmed with individuals wanting to be vaccinated. Certain local public health departments in California, including the Santa Clara County Public Health Department, provided chairs and extra water for people waiting in long lines outdoors in warm weather. Fear of a more virulent pandemic influenza strain could exacerbate such scenarios. A number of states reported that they did not have the capacity to immunize large numbers of people and partnered with other organizations to increase their capacity. For example, in 2004-05, according to state health officials in Florida, county health departments, including those in Orange and Broward Counties, worked with a national home health organization to immunize high risk individuals by holding mass immunization clinics and setting up clinics in providers’ offices to help administer available vaccine quickly. Other locations, including the local health department in Portland, Maine, held lotteries for available vaccine; according to local health officials, however, administrative time was required to arrange and publicize the lottery.

HHS’s draft pandemic plan does not define priority groups for vaccination, although the plan states that HHS is developing an initial list of suggested priority groups and soliciting public comment on the list. The draft plan instructs the states to define priority groups for early vaccination and indicates that as information about virus severity becomes available,
recommendations will be formulated at the national level. According to the plan, setting priorities will be iterative, tied to vaccine availability and the pandemic’s progression. Without agreed-upon identification of potential priority groups in advance, however, problems can arise. During the 2004–05 season, for example, CDC and ACIP acted quickly on October 5, 2004, to narrow the priority groups for available vaccine, giving the narrowed groups equal importance. In some places, however, there was not enough available vaccine to cover everyone in these narrowed groups, so states set their own priorities among these groups. Maine, for example, excluded health care workers from the state’s early priority groups because state officials estimated that there was not enough vaccine to cover everyone in CDC and ACIP’s priority groups.

Communicating Information about the Situation and Response Plan Clearly and Effectively

Another challenge in responding to a pandemic will be to clearly communicate information about the situation and the nation’s response plans to public health officials, providers, and the public. Experience during the 2004–05 vaccine shortage illustrates the critical role communication plays when information about vaccine supply is unclear. Communicating a consistent message and clearly explaining any apparent inconsistencies. In a pandemic, clear communication on who should be vaccinated will be important, particularly if the priority population differs from those targeted for annual influenza vaccination, or if the priority groups in one area of the country differ from those in others. During the 2004–05 influenza season, health officials in Minnesota reported that some confusion resulted when the state determined that...

On October 5, 2004, CDC, in coordination with ACIP, issued interim recommendations for influenza vaccination during the 2004–05 season that took precedence over prior recommendations. The season’s priority groups for vaccination with injectable influenza vaccine were considered to be of equal importance. They included all children aged 6–23 months, adults aged 65 years and older, persons aged 2–64 years with underlying chronic medical conditions, all women who would be pregnant during the influenza season, residents of nursing homes and long-term care facilities, children aged 6 months–18 years on chronic aspirin therapy, health care workers involved in direct patient care, and out-of-home caregivers and household contacts of children younger than 6 months. See Centers for Disease Control and Prevention, “Influenza Vaccination Recommendations, 2004–05 Influenza Season,” Morbidity and Mortality Weekly Report, vol. 53, no. 39 (2004): 833–834.

According to CDC officials, as part of preparations for the 2005–06 influenza season, the agency is preparing communication strategies with appropriate messages to respond to the fluctuations in supply and demand anticipated throughout the season. CDC has developed the communication plan but has not released the plan, so it is in the clearance process.
vaccine was sufficient to meet demand among the state’s narrower priority groups and made vaccine available to other groups, such as healthy individuals aged 65–64 years, earlier than recommended by CDC. Health officials in California reported a similar situation. State health officials pointed out that in mid-December, local radio stations in California were running two public service announcements—one from CDC advising those 65 and older to be vaccinated and one from the California Department of Health Services advising those 50 and older to be vaccinated. State officials emphasized that these mixed messages created confusion.

- **Communicating information from a primary source.** Having a primary and timely source of information will be important in a pandemic. In the 2004–05 influenza season, individuals seeking vaccine could have found themselves in a communication loop that provided no answers. For example, CDC advised people seeking influenza vaccine to contact their local public health department; in some cases however, individuals calling the local public health department would be told to call their primary care provider, and when they called their primary care provider, they would be told to call their local public health department. This lack of a reliable source of information led to confusion and possibly to high-risk individuals giving up and not receiving the protection of an annual influenza vaccination.8

- **Recognizing that different communication mechanisms are important and require resources.** Another challenge in communicating plans in the event of a pandemic will be to ensure that the communication mechanisms used reach all affected populations. During the 2004–05 influenza season, public health officials reported the importance of different methods of communication. For example, officials from the Seattle–King County Public Health Department in Washington State reported that it was important to have a hotline as well as an information posted on a Web site, because some seniors calling Seattle–King County’s hotline reported that they did not have access to the Internet. According to state and local health officials, however, maintaining these communication mechanisms took time and strained personnel resources. In Minnesota, for example, to supplement state employees, the state health department.

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asked public health nursing students to volunteer to staff the state’s influenza vaccine hotline.

- Educating health care providers and the public about all available vaccines. For the 2004-05 season, approximately 3 million doses of nasal spray vaccine were ultimately available for vaccinating healthy individuals aged 5-65 years who were not pregnant, including some individuals (such as health care workers in this age group and household contacts of children younger than 6 months) in the priority groups defined by CDC and ACIP, yet some of these individuals were reluctant to use this vaccine because they feared that the live virus in the nasal spray could be transmitted to others. State health officials in Maine, for example, reported that the state purchased about 1,500 doses of the nasal spray vaccine for their emergency medical service personnel and health care workers, yet administered only 500 doses.

### Ensuring Supply of Influenza Vaccine and Antiviral Drugs

Challenges in ensuring an adequate and timely supply of influenza vaccine and antiviral drugs—which can help prevent or mitigate the number of influenza-related deaths until an pandemic influenza vaccine becomes available—may be exacerbated during an influenza pandemic. Particularly given the time needed to produce vaccines, influenza vaccine may be unavailable or in short supply and may not be widely available during the initial stages of a pandemic. According to CDC, maintaining an abundant annual influenza vaccine supply is critically important for protecting the public’s health and improving our preparedness for an influenza pandemic. The shortages of influenza vaccine in 2004-05 and previous seasons have highlighted the fragility of the influenza vaccine market and the need for its expansion and stabilization.

In its budget request for fiscal year 2006, CDC reports that it plans to take steps to ensure an expanded influenza vaccine supply. The agency’s fiscal year 2006 budget request includes $30 million for CDC to enter into guaranteed-purchase contracts with vaccine manufacturers to ensure the production of bulk monovalent influenza vaccine. If supplies fall short, this bulk product can be turned into a finished trivalent influenza vaccine product for annual distribution. If supplies are sufficient, the bulk vaccine can be held until the following year’s influenza season and developed into finished vaccines if the bulk products maintain their

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Footnote: Monovalent influenza vaccine protects against a single strain of influenza; trivalent influenza vaccine protects against three strains of influenza.
potency and the circulating strains remain the same. According to CDC, this guarantee will help expand the influenza market by providing an incentive to manufacturers to expand capacity and possibly encourage additional manufacturers to enter the market. In addition, CDC’s fiscal year 2006 budget request includes an increase of $20 million to support influenza vaccine purchase activities.\footnote{The $20 million increase is for CDC’s Immunization Grant Program that provides vaccines for children, adolescents, and adults who present primarily at local health departments but are not eligible for CDC’s Vaccines for Children program.}

In the event of a pandemic, before a vaccine is available or during a period of limited vaccine supply, use of antiviral drugs could have a significant effect. Antiviral drugs can be used against all strains of pandemic influenza and, because they can be manufactured and stored before they are needed, could be available both to prevent illness and, if administered within 48 hours after symptoms begin, to treat it. Like vaccine, antiviral drugs take several months to produce from raw materials, and according to one antiviral drug manufacturer, the lead time needed to scale up production capacity and build stockpiles may make it difficult to meet any large-scale, unanticipated demand immediately. HHS’ National Vaccine Program Office also reported that in a pandemic, the manufacturing capacity and supply of antiviral drugs is likely to be less than the global demand. For these reasons, the National Vaccine Program Office reported that analysis is under way to determine optimal strategies for antiviral drug use when supplies are suboptimal; the office also noted that antiviral drugs have been included in the national stockpile. HHS has purchased more than 7 million doses of antiviral drugs for the national stockpile.

Nevertheless, this stockpile is limited, and it is unclear how much will be available in the event of a pandemic, given existing production capacity. Moreover, some influenza virus strains can become resistant to one or more of the four approved influenza antiviral drugs, and thus the drugs may not always work. For example, the avian influenza virus strain (H5N1) identified in human patients in Asia in 2004 and 2006 has been resistant to two of four existing antiviral drugs.
Hospital and Workforce Capacity to Respond to Large-Scale Infectious Disease Outbreaks

The lack of sufficient hospital and workforce capacity is another challenge that may affect response efforts during an influenza pandemic. The lack of sufficient capacity could be more severe during an influenza pandemic compared with other natural disasters, such as a tornado or hurricane, or with an intentional release of a bioterrorist agent because it is likely that a pandemic would result in widespread and sustained effects. Public health officials we spoke with said that a large-scale outbreak, such as an influenza pandemic, could strain the available capacity of hospitals by requiring entire hospital sections, along with their staff, to be used as isolation facilities. In addition, most states lack surge capacity—the ability to respond to the large influx of patients that occurs during a public health emergency. For example, few states reported having the capacity to evaluate, diagnose, and treat 500 or more patients involved in a single incident. In addition, few states reported having the capacity to rapidly establish clinics to immunize or treat large numbers of patients. Moreover, shortages in the health care workforce could occur during an influenza pandemic because higher disease rates could result in high rates of absenteeism among workers who are likely to be at increased risk of exposure and illness or who may need to care for ill family members.

Concluding Observations

Important challenges remain in the nation’s preparedness and response should an influenza pandemic occur in the United States. As we learned in the 2004-05 influenza season, when vaccine supply, relative to demand, is limited, planning and effective communication are critical to ensure timely delivery of vaccine to those who need it. HHS’s current draft plan lacks some key information for planning our nation’s response to a pandemic. It is important for the federal government and the states to work through critical issues—such as how vaccine will be purchased, distributed, and administered; which population groups are likely to have priority for vaccination; what communication strategies are most effective; and how to address issues related to vaccine and antiviral supply and hospital and workforce capacity—before we are in a time of crisis. Although HHS contends that agency flexibility is needed during a pandemic, until key federal decisions are made, public health officials at all levels may find it difficult to plan for an influenza pandemic, and the timeliness and adequacy of response efforts may be compromised.

Mr. Chairman, this concludes my prepared statement. I would be happy to respond to any questions you or other Members of the Committee may have at this time.
GAO Contact and Staff Acknowledgments

For further information about this testimony, please contact Marcia Crosse at (202) 512-7110. Jennifer Major, Nick Larson, Gap Hee Lee, Kim Yamane, George Bogart, and Ellen W. Chu made key contributions to this statement.
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Washington, D.C. 20548
Mr. SHAYS. Thank you very much for your statement, Dr. Crosse.
Ms. Selecky.

STATEMENT OF MARY C. SELECKY

Ms. SELECKY. Thank you, Mr. Chairman and distinguished members of the House Government Reform Committee. I am Mary Selecky, Washington State Secretary of Health, and I am testifying in front of you on behalf of the Association of State and Territorial Health Officials [ASTHO]. I would like to thank the Chair and the committee for continuing to focus attention on our Nation’s preparedness levels and our ability to respond to a flu pandemic.

In the last year, my colleagues from Virginia and Arkansas have testified before this committee about the challenges public health leaders across the Nation faced during this past year’s flu season. My colleagues suggested three actions that the Federal Government should consider to avoid a repeat of last year’s situation: first, the development of a national plan to deal with vaccine shortages; second, the establishment of a Vaccine for Adults Program; third, the expansion of funding for the Centers for Disease Control and Prevention’s National Immunization Program. These three actions will help ensure that all our underserved citizens receive the vaccines they need and allow States and localities to enhance adult immunization programs. ASTHO continues to strongly urge the Congress and the administration to support these efforts.

I would like to focus my remarks on pandemic flu preparedness. Lessons learned from last annual influenza season, the history of influenza pandemics, and the 2001 anthrax attacks continue to underscore the need for public health preparedness. Health officials must have overall preparedness plans in place, an advanced understanding of our unique role during an influenza pandemic, and a knowledge of the resources available to help us protect the public.

State health officials will be looked to as controlling health authorities by Governors, legislatures, and the public they all serve. State and local health officials will need to assert significant leadership to mobilize and sustain private and public healthcare response during an influenza pandemic.

It will take Federal, State, and local public health agencies working cooperatively to deal effectively and efficiently with a public health concern of this magnitude. To date, the collaboration has been good.

We do remain concerned, however, that public health agencies have been asked to take on pandemic flu activities on top of existing priorities already established for the preparedness cooperative agreements. If the Federal Government is truly committed to enhancing our pandemic flu response, we need significant increases in resources for State and local efforts. All the preventive and therapeutic measures in the world are useless without the ability to get them to those who desperately need them.

Development of national guidelines is critically important to ensure consistent response. However, they must be flexible in order to meet State needs.

There is already significant work going on. ASTHO, our organization, produced in 2002 a preparedness planning for State health officials on pandemic influenza. States are required to have our
pandemic flu plans completed in July 2005, and Washington State
completed ours in April. This has been very difficult because the
Federal plan hasn't been completed, as you have heard.

Having a good plan is the first step. But exercising the plans to
see what works and what needs to be improved is just as impor-
tant.

In Washington State, we recently conducted a pandemic flu ta-
bletop exercise with our neighbors to the north in Vancouver, Brit-
ish Columbia. In addition, Public Health Seattle King County, our
largest local health jurisdiction, held a pandemic tabletop exercise
with major healthcare facilities in the community as well as other
county agencies.

We have unprecedented opportunity to improve the Nation’s re-
sponse to flu pandemic. This is an integral part of our overall pre-
paredness. It is impossible to predict when a pandemic will occur
and challenge us. But this is the wrong time for the Federal Gov-
ernment to cut State and local preparedness funding by $130 mil-

lion, when we are to address this national priority issue.

States have plans for potential public health threats, including
pandemic flu. We are exercising those plans. We will continue to
improve upon them. We are making progress. Are we fully pre-
pared? Absolutely not. We are more prepared today than we were
several years ago, but not prepared enough.

The new Trust for America’s Health report estimates that more
than half a million Americans may die in a pandemic. Our families,
our neighbors, and all the people of this country expect us to be
ready when the time comes. I have no doubt that the work we are
doing at the State and local level, as well as with our Federal col-
leagues, will help us save lives tomorrow. Please help us make sure
we have the resources to get the job done.

In closing, let me reiterate four important points: pandemic flu
preparedness is a critical issue for public health to address as part
of its overall prevention, detection, and response efforts to any nat-
ural or terrorist event; collaboration among all levels of govern-
mental public health is essential; reducing Federal funding for pre-
paredness is exactly the wrong thing to do at this time—a sus-
tained Federal commitment to preparedness is vital—and progress
has been made, but there is much more to be done.

The public health community stands ready to work with you to
address this threat, but we need your help and support.

I would be pleased to answer any questions you might have.

Thank you, Mr. Chairman.

[The prepared statement of Ms. Selecky follows:]
Statement of

MARY C. SELECKY
SECRETARY
WASHINGTON STATE DEPARTMENT OF HEALTH

Before the

UNITED STATES HOUSE OF REPRESENTATIVES

GOVERNMENT REFORM COMMITTEE

JUNE 30, 2005

Representing

THE ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICIALS
(ASTHO)
Mr. Chairman and distinguished members of the House Government Reform Committee,
I am Mary C. Selecky, Secretary of the Washington State Department of Health, and I am
honored to be appearing before you today on behalf of the Association of State and
Territorial Health Officials (ASTHO). I would like to thank the Chair and the Committee
members for continuing to focus attention on our nation’s preparedness levels and our
ability to respond to a flu pandemic.

In the last year, my colleagues from Virginia and Arkansas have testified before this
committee about the challenges public health leaders across the nation faced during this
past year’s flu season.

My colleagues suggested three actions that the federal government should consider to
avoid a repeat of last year’s situation – 1) development of a national plan to deal with
vaccine shortages; 2) establishment of a Vaccine For Adults Program; and 3) expansion
of funding for the Centers for Disease Control and Prevention’s (CDC) National
Immunization Program. These three actions will help to ensure that all our underserved
citizens receive the vaccines they need and allow states and localities to enhance adult
immunization programs. ASTHO continues to strongly urge the Congress and the
Administration to support these efforts.

I would like to focus my remarks on pandemic flu preparedness.

Lessons learned from the last annual influenza season, the history of influenza
pandemics, and the 2001 anthrax attacks continue to underscore the need for public
health preparedness. Health officials must have overall preparedness plans in place, an advanced understanding of our unique role during an influenza pandemic, and a knowledge of the resources available to us to protect the public. State health officials will be looked to as a controlling health authority by governors, legislatures, and the public they all serve; state and local health officials will need to assert significant leadership to mobilize and sustain private and public healthcare response during an influenza pandemic.

It will take federal, state and local public health agencies working cooperatively to deal effectively and efficiently with a public health concern of this magnitude; to date, that collaboration has been good.

We do remain concerned, however, that public health agencies have been asked to take on pandemic flu activities on top of existing priorities already established for the federal preparedness cooperative agreement funding. If the federal government is truly committed to enhancing our pandemic flu response, we need significant increases in resources for state and local efforts. Vaccines and antivirals are an important part of the answer, but not nearly enough by themselves. All the preventive and therapeutic measures in the world are useless without the ability to get them to those who desperately need them.

Development of national guidelines is critically important to ensure a consistent response across the country. However, these guidelines must be flexible enough to allow each state to address its specific needs and essential services.
There is already significant work going on at the state level. States are required to have pandemic flu plans completed in July 2005. This has been very difficult because the federal plan hasn’t been completed and is unavailable for use as a guide for state planners.

Having a plan is a good first step. Exercising those plans to see what works and what needs to be improved upon is just as important. In Washington State, we recently conducted a pandemic flu tabletop exercise with our neighbors to the north in Vancouver, British Columbia, Canada. In addition, Public Health Seattle King County, our largest local health jurisdiction, held a pandemic tabletop exercise with major health care facilities in the community, as well as other county agencies.

We have an unprecedented opportunity to improve the nation’s response to future pandemics. Pandemic flu preparedness must be an integral part of overall preparedness. It is impossible to predict when the next influenza pandemic will occur and challenge us to respond. We must now devote significant time and resources to addressing this priority issue. This is exactly the wrong time for the federal government to cut state and local preparedness funding by $130 million.

States have plans for many potential public health threats including pandemic flu. We are exercising those plans and will continue to improve upon them. We are making progress. Are we fully prepared to respond to an influenza pandemic? Absolutely not! We are more prepared today than we were several years ago, but we are not prepared enough.
The new Trust for America's Health report estimates more than half a million Americans may die in a pandemic. Our families, our neighbors, and all the people of this country expect us to be ready when that time comes. I have no doubt that the work we do today can save lives tomorrow. Please help us make sure we have the resources to get the job done right.

In closing, let me reiterate four important points: 1) Pandemic flu preparedness is a critical issue for public health to address as part of its overall prevention, detection, and response efforts for any natural or terrorist event; 2) Collaboration among all levels of governmental public health is essential for influenza pandemic preparedness; 3) Reducing federal funding for preparedness is exactly the wrong thing to do at this time—a sustained federal commitment to preparedness is vital; and, 4) Progress has been made, but there is much more to be done.

The public health community stands ready to work with you to address this threat. We need your help and your support.

I would be pleased to answer any questions you might have.
Chairman Tom Davis. Thank you very much.
Dr. Hearne. Thanks for being with us.

STATEMENT OF DR. SHELLEY A. HEARNE

Dr. HEARNE. Thank you, Mr. Chairman and members of the committee, thanks for this opportunity to present our views on preparedness.

Let me just say thank you again for being here to present our views on the potentials of what a deadly and massive novel virus could do if it hit this country. As a national organization that is dedicated to preventing epidemics and protecting people, Trust for America’s Health provides the independent oversight on our Nation’s public health system, that is, the front lines in a pandemic.

What we have been talking about here today is that a pandemic is actually potentially even more threatening than bioterrorism attacks, and worse is experts believe it is inevitable. Yet, what we do know is that with proactive coordinated actions, this Nation could be taking lifesaving efforts today to mitigate the devastating impact.

What I would like to do is submit for the record our just-released report “The Killer Flu?” What this report does is provide a State-by-State examination of how many people may die, how many may be hospitalized during a pandemic. It also includes a review of the United States and State preparedness, and a series of recommendations for improving readiness.

Chairman Tom Davis. And, without objection, that will be put in the record.

[NOTE.—The information referred to is on file with the committee.]

Dr. HEARNE. Thank you, Mr. Chairman.

Let me summarize. That report finds that there is a failure to establish a cohesive, rapid, and, most importantly, transparent U.S. pandemic strategy, which puts Americans needlessly at risk. I would like to highlight three shortcomings for you and offer some concrete suggestions on how we can actually improve the Nation’s response capacity.

First, a final and operational pandemic plan must become a priority for this administration. The good news is, as was discussed, HHS has released a draft plan last August. Bad news is it is draft and with no formal deadline for completion. TFAH has actually reviewed the majority of State pandemic plans and found widely different stages of readiness.

It is no surprise, as we have discussed, since there isn’t Federal guidance out there. What we have found is that most of these plans are simply plans for plans. Some States are not making those plans public, which many experts believe is going to harm our ability to fully integrate and create trust with the public, healthcare providers, and the critical first responders that would be part of a pandemic response.

To ensure nationwide preparedness standards and to facilitate a regional coordination, much like what Ms. Selecky was talking about, we need to have CDC formally reviewing and approving all State plans, and to require that these are public documents. All these plans must have greater specificity, which also was discussed
in terms of things like who are the high priority populations that would get the limited medicines and vaccines during a pandemic. Is it the healthcare workers and their families, utility operators, police, firemen?

These are the kinds of issues that we need to determine prior to an outbreak, not in the midst of crisis. Last year’s flu vaccine shortage was an ugly glimpse into the lack of planning and preparedness.

And the Federal pandemic plan cannot just be a game plan for the health world. Unlike other nations, the United States does not appear to have assessed or planned how a pandemic would actually disrupt the economy and society with potential school and workplace closures and travel restrictions. The President should designate a senior official—you should have an answer when you ask who is in charge—that is responsible for ensuring that cabinet level coordination of the Federal Government’s response to a pandemic.

The second issue I want to touch on is getting this Nation positioned to rapidly provide vaccines to all Americans. We are behind the eight ball because of our Nation’s limited and antiquated capacity. Most experts estimate on the extensive lag time that would be existing for getting vaccines. First thing we should be thinking about: the FDA needs to immediately begin work with potential manufacturers of a vaccine to develop in advance the criteria for a rapid response approval.

We are also concerned about the U.S. domestic production capacity. With a projected stockpile of 40 million doses as a start, we need to be able to vaccinate the entire U.S. population. What HHS should be doing is investigating the value of creating a reserve manufacturing capacity here in the United States, similar to what Canada has done. This would be especially important if the pandemic is not this avian flu, which means that the current stockpile that we have of H5N1 would be ineffective.

Third, we need to assure that our stockpile of medical supplies and medicines—which many of these are being produced overseas, and with a healthcare system that relies on a “just in time” inventory—we need to be looking at how to make sure the stockpile is built faster and is large enough to cover us in the time of need.

For example, the United States is very late and very short in purchasing significant quantities of Tamiflu. Other countries have followed the who estimates of a pandemic effecting at least 25 percent of the population, and they have ordered that much. The United States is somewhere below 2 percent.

Vaccines and antivirals are not the only stockpile needs. We need to be talking about ventilators, masks, vaccines, even the vaccine injection devices that were brought up earlier.

We are also deeply concerned about the current licensing dispute that is going on between Gilead and Roche, and making sure that this does not result in a reduction of the production of Tamiflu. We urge the administration to aggressively step in and work with these companies to make sure current capacity is maintained and that we actually increase domestic operations in the immediate future.

The administration and Congress must find the sufficient funding in the coming years to increase the stockpiles and create incen-
tives for U.S.-based production. But I cannot emphasize more strongly enough the point that ASTHO and others have raised, that these pandemic activities need to be supported at all levels, but not come at the expense of other preparedness efforts. The Nation’s stockpile, the preparedness activities, the bioterrorism readiness, these have to be done in a fully integrated fashion, not in separate silos and not syphoning off dollars to take care of each other.

In summary, there are several steps that we need to take today to improve readiness. It can’t be a paper chase, it needs to be a priority. Thank you for the time.

[The prepared statement of Dr. Hearne follows:]
Written Testimony of

Shelley Hearne, DrPH
Executive Director
Trust for America’s Health

Submitted to

U.S. House of Representatives
Committee on Government Reform

June 30, 2005

The Next Flu Pandemic: Evaluating U.S. Readiness

For further information:
Richard S. Hamburg
Director of Government Relations
Trust for America’s Health
202-223-9876 (ph)
rhamburg@tfah.org
Mr. Chairman and members of the Committee, thank you for the opportunity to provide our views on The Next Flu Pandemic: Evaluating U.S. Readiness. As a non-profit, non-partisan organization dedicated to saving lives by protecting the health of every community and working to make disease prevention a national priority, Trust for America's Health (TFAH) maintains that proactive, coordinated public health actions can help mitigate the impact of a pandemic influenza outbreak.

TFAH has just released a report, "The Killer Flu?" that provides a state-by-state examination of potential deaths and hospitalizations due to a flu pandemic based on model estimates; a state-by-state examination of capacity to treat citizens with recommended antivirals based on model estimates; a review of United States and state pandemic readiness, including a comparison to other nations' progress; and recommendations for improved pandemic readiness. I would like to submit the report in its entirety for the hearing record.

Overall, the report finds that despite the health and economic implications of such an event, pandemic planning efforts are lagging in the U.S., especially when compared to the United Kingdom (U.K.) and Canada.

The report also points out that the U.S. has not assessed or planned for the disruption a flu pandemic could cause both to the economy and society as a whole. This includes daily life considerations, such as potential school and workplace closures, potential travel and mass transit restrictions, and the potential need to close businesses resulting in complications in the delivery of food and basic supplies to people. Daily life and economic problems would likely emerge in the U.S. even before the pandemic flu hit the country due to the global interdependence of the world economy.

An equally troubling finding establishes that aspects of the planning process, such as ensuring vaccine and antiviral capabilities and surge capacity readiness, are incomplete or fragmented.

Mr. Chairman, TFAH maintains that the failure to establish a cohesive, rapid, and transparent U.S. pandemic strategy could prove a major weakness against a virulent and efficient virus -- putting Americans needlessly at risk.

That is why we believe that Congress and the Administration must take steps now to ensure that the nation’s public health system and the health care delivery system will be able to respond to a major health crisis -- even beyond some of our fears of bioterrorism or chemical terrorism. While experts predict a pandemic flu may be "inevitable," subsequent death rates predicted to be in the millions are not. What will make the difference? We need strong, directed and rapid federal leadership, we must convert national and state pandemic influenza plans into operational blueprints, and we should increase vaccine production and capacity, procure adequate vaccines and antivirals for treatment, and stockpile additional medical supplies and equipment.
Pandemic Readiness: Moving from Planning to Action

Mr. Chairman, simply put, U.S. pandemic influenza preparedness is inadequate. Both the federal pandemic plan and various state pandemic plans are insufficient blueprints for an effective national response to a pandemic influenza.

Although a positive first step, the federal pandemic flu plan issued last August by the Department of Health and Human Services (DHHS) is still a draft. Moreover, the draft plan lacks specificity in several key areas, which were enumerated in comments received by the Department during the public comment period. TFAH believes that a final pandemic influenza plan must become a priority for this Administration and should provide the operational blueprint for the six pandemic phases as defined by the World Health Organization (WHO).

At the state level, most public health agencies have developed draft pandemic response plans, but they are in widely different phases of readiness. Many states have asked for additional and more specific guidance from the DHHS. Some are refusing to make their plans public even though many experts believe that public availability of plans is essential to improve integration with other jurisdictions, health care providers, and first responders.

TFAH believes that the Centers for Disease Control and Prevention (CDC) should formally review and approve state pandemic influenza plans in order to ensure nationwide preparedness standards and to facilitate regional coordination. Further, we urge CDC to require states to make approved plans publicly available. Perhaps most importantly, TFAH believes that pandemic flu preparedness activities at the federal, state and local levels should be supported with specific funding and not come at the expense of other preparedness efforts.

At the beginning of a pandemic, there may be an insufficient supply of vaccines and antivirals. A key element of pandemic planning is to determine protocols for allocation of vaccines and medicines among high priority populations, such as health care workers and public safety workers, prior to an outbreak.

As we learned last winter, prioritization is also important for the annual flu, when vaccine is in short supply. With the recent announcement by Chiron that its manufacturing capacity for this year’s influenza vaccine will fall short, it would be prudent for CDC and DHHS officials to provide specific guidance now to states’ health agencies as to which sectors of the population should receive antiviral medications and vaccines. In addition, CDC should immediately put into place measures that would assure equal geographic access to vaccines so that the nation does not face a shortage of annual influenza vaccine, with some states having excess supply and others unable to meet the demand for high-risk groups. This would help prevent the widespread confusion, long lines of worried elderly Americans, and the vaccine distribution issues that plagued last year’s flu season.

With respect to federal leadership, TFAH urges the President to designate a senior official, whose primary responsibility is to assure Cabinet-level coordination of the federal government’s response to a pandemic and also to ensure coordination between civil society (non-governmental economic infrastructure) and government during a pandemic.
Ultimately, there should be a government-wide pandemic preparedness plan, not just one that centers on health-related matters and DHHS activities.

Further, we believe that the CDC, in consultation with other federal agencies, should develop and implement a public education campaign about pandemic influenza and preparedness, including information on the potential need for general vaccination and personal precautionary measures. The agency should also develop a plan for communicating with the business community to provide information about the potential economic consequences of a pandemic, including the possibility of mass absenteeism and the potential need to convert certain facilities (e.g. hotels) as surge capacity treatment centers.

**Stockpiling Vaccines, Medicines, Medical Supplies and Equipment**

Building a stockpile for a pandemic is a responsible public health measure and TFAH maintains that adequate preparedness includes stockpiling both a vaccine and antivirals. However, we remain deeply concerned that the stockpiles will not be built fast enough and will not be large enough.

The U.S. is very late in entering the market for significant bulk purchase of Tamiflu, an antiviral that can treat symptoms of influenza and reduce the severity of the infection. With current production capacity, it could be sometime in 2007 before the stockpile ordered today is available. Most Tamiflu is produced abroad and requires nearly one year to manufacture. We believe that the Department should take immediate steps to work with industry to increase domestic production capacity, to assure that the stockpile is built quickly, and to assure that in the event of a pandemic Tamiflu will continue to be available to Americans.

It is also not clear that the amount of Tamiflu ordered is sufficient to address the demand in a pandemic. Other countries are following WHO estimates of a pandemic affecting at least 25 percent of the population, and have ordered enough Tamiflu to treat all who might be sick. This would translate to over 70 million courses in the United States. Some, such as the Infectious Diseases Society of America, have called for stockpiling as much as 124 million courses of Tamiflu for treatment and prevention of avian flu.

TFAH remains even more concerned about vaccine production capacity. In a pandemic, we can target antiviral treatment to those who are already sick, but must provide vaccines to all who are at risk -- which in this case would be all Americans. It is not at all clear that U.S. domestic vaccine producers could rapidly manufacture hundreds of millions of doses of a pandemic flu vaccine.

Most experts estimate there will be a lag time of six to nine months before a vaccine can be produced in sufficient quantities to protect individuals against a pandemic strain of influenza to which most people will have no natural immunity. While issues around vaccine manufacturing, distribution, safety and access are complex, other nations are putting protocols in place now with respect to creating a rapid response approval process for a pandemic flu vaccine. For example, regulators in the U.K. are already working with vaccine manufacturers to develop a model application for approval of a pandemic vaccine.
TFAH believes that the Food and Drug Administration (FDA) should immediately begin work with potential manufacturers of a pandemic flu vaccine to develop in advance the specific criteria for rapid response approval of a pandemic vaccine, which might save a month or two in the time it takes from identifying the flu strain and having the capacity to vaccinate Americans.

We are also concerned about whether the U.S. has sufficient domestic production capacity for a pandemic flu vaccine. While a projected initial stockpile of 40 million doses is a start, we would need to be able to vaccinate the entire U.S. population against a pandemic strain. Only about half of the U.S. annual flu vaccine supply is generated within the U.S.; in a pandemic, products manufactured elsewhere may not be available to us. We believe DHHS should investigate the value of creating a reserve production capacity to assure rapid ramp up of production, something the Canadian government has contracted for in the event of a pandemic. This would be especially important in the event the pandemic strain is not avian flu, which means the current H5N1 stockpile would not be effective.

Therefore, we hope the Administration will work with Congress to find sufficient funding in Fiscal Year (FY) 2006 to increase stockpiles to true preparedness levels and create incentives for industry to increase U.S.-based Tamiflu and vaccine production.

Vaccines and antivirals are not the only supplies that need to be stockpiled in preparation for a pandemic. Federal officials should also address the need to stockpile medical supplies that will be necessary to combat a pandemic. Currently, most health providers order and stock supplies on a “just-in-time” basis. This means they often have only a few days of reserve supplies, equipment, and medicines, including many basic protective items such as masks, gloves, gowns, and clean hospital linens, many of which are produced in Asia, which may be the epicenter of a pandemic. That’s why we believe steps must be taken immediately to stockpile additional supplies, particularly since during an outbreak, many production and delivery systems for supplies will likely be stalled or even stopped.

Additional Recommendations

“A Killer Flu” details a series of specific recommendations that would bolster U.S. readiness to combat an influenza pandemic. In addition to the recommendations related to operationalizing pandemic plans, government-wide coordination and leadership, vaccine production and the need to stockpile vaccines, antivirals and medical supplies, TFAH believes that Congress, the Administration and state health officials should take the following actions:

- **Define Roles and Responsibilities**

  A clearly-defined organizational structure and chain of command is essential for rapid and efficient control and response, both in the federal government and at the state and local levels. Immediate planning should be occurring at the federal level to minimize disruption of the health care system and the overall economy. States must define and agree upon leadership roles and responsibilities with respect to who is in charge of a state’s public health and health care decisions. Plans must also designate liaisons to work with other jurisdictions and federal officials.
• Outbreak Tracking

Plans should ensure adequate laboratory surveillance of influenza, including the ability to isolate and subtype influenza viruses year round. Following federal guidelines outlined by DHHS, states should report all necessary data and information to federal and other health officials as soon as it becomes available. Congress should provide additional support for CDC’s global surveillance activities, and the U.S. should support the WHO’s surveillance program to assure as early a warning as possible for U.S. preparedness purposes.

• Vaccine Research, Development, and Production

The U.S. should continue to support and expand research into new technologies for influenza vaccine and clinical trials for potential avian flu and other pandemic vaccines. While the U.S. has issued limited contracts for stockpiling a potential pandemic vaccine, the federal government should also explore the Canadian approach of contracting for a reserve production capacity located in the U.S. A vaccine stockpiling approach is successful if public health authorities have guessed correctly on what the pandemic strain will be. A reserve production capacity can assure quick turnaround for production of a vaccine for the actual pandemic strain.

• Mass Vaccination and Treatment Systems

The federal government, in coordination with the states, must develop systems for tracking and distributing antiviral medication and vaccines. A national system is needed to assure targeted and/or equitable distribution of supply, so we do not have a repeat of the 2004-2005 flu season distribution problems. State-level systems also are needed to assure similar availability across a state. One of the best ways to improve vaccination preparations for a pandemic outbreak may be to enhance annual flu vaccination coverage for non-traditional high-risk groups (e.g. individuals with chronic diseases or compromised immune systems) to facilitate access to these populations.

• Public Information Campaigns and Materials

Communicating with the public in a clear and efficient manner is essential during a high-anxiety time. The federal government, in conjunction with the states, should develop coordinated messages for various audiences (media, public, providers, etc.) for each stage of a potential pandemic. States must identify and train spokespersons in multiple languages and educate public health officials, politicians, community leaders, partners, and the media about what information will and will not be available during a pandemic. States should ensure clear and consistent messaging by creating information templates in multiple languages ready for customization and distribution during a pandemic.
• **Surge Capacity Capabilities**

Plans must account for the likelihood that hospitals will be quickly overwhelmed during a pandemic, by developing auxiliary sites such as shelters, schools, nursing homes, hotels, and daycare centers for surge capacity treatment and for treatment of the “walking well.” States should be conducting surveys of potential sites and obtaining agreements.

• **Secure a Backup Workforce**

States should conduct and maintain an inventory of healthcare professional residents, including current and retired doctors, nurses, veterinarians, emergency medical staff, and other potential volunteers. These workers could be an essential expanded workforce during a pandemic. Pandemic survivors are also a population of potential workers. States should plan for tracking and soliciting volunteer support from this population, which is presumably immune to the virus.

• **Ensure Availability of Food, Water, and Other Supplies**

States must account for high demand for food, water, and other basic supplies, and plan for distribution to general and hard-to-reach populations. Plans should factor in potential complications that include: infected food and delivery workers, possible infected store facilities, and limitations on public interaction both for those infected and the general population at risk of exposure. Planners must also weigh the issue of "just-in-time" manufacturing of food and supplies, since reserves of supplies will not be available. Additionally, planners must address the limitations of medical equipment manufacturing, much of which Asia exports to the world.

• **Quarantine Measures and Authority to Close Public Places**

States must establish clear legal authority and emergency measures to effectively contain the spread of disease. States must have powers to prohibit public gatherings, close public facilities and schools, and restrict travel, if necessary.

• **Measures to Manage Mass Death**

Planning for worst-case scenarios is a critical component of effective planning. States must conduct and maintain an inventory of facilities with sufficient refrigerated storage to serve as temporary morgues in the event of a pandemic.

Such policies and investments will help stabilize the nation’s health and economy in the event of a pandemic while ensuring that pandemic readiness preparations are “commensurate with the scale of the threat we face.”

I thank you again for this opportunity to express TFAH’s views on evaluating U.S. readiness for the next flu pandemic.
Chairman Tom Davis. Thank you very much.
Dr. Milligan, thank you for being with us.

STATEMENT OF DR. JOHN F. MILLIGAN

Dr. Milligan. Mr. Chairman, Congressman Waxman, and committee members, thank you for the invitation to present here today. I am John Milligan, executive vice president and CFO of Gilead Sciences. By way of background, I am a Ph.D. biochemist, and I was a project team leader for the development of Tamiflu by Gilead.

Gilead is a biopharmaceutical company headquartered in Foster City, CA, the district of Congressman Tom Lantos. We also have research facilities in Durham, NC; a manufacturing facility in San Dimas, CA; and overseas offices throughout Europe and Australia.

Since Gilead was founded nearly 20 years ago, the company has focused on advancing the care of patients suffering from life-threatening diseases. Over the course of our company's history, Gilead has successfully developed, commercialized, and ensured broad access to a portfolio of antiviral medicines in HIV and hepatitis.

Today, these important antivirals are improving the quality of life for patients around the globe. Gilead does not achieve this alone, but through a strong commitment to collaboration, working in partnership within our industry, with governments, with healthcare professionals, and with nongovernmental organizations.

As you know, Gilead is the inventor of Tamiflu, or oseltamivir phosphate. Tamiflu is the first and only antiviral pill available for the treatment and prevention of all common strains of influenza A and B. The compound was shown to be active in animal models against avian flu, also known as H5N1 strain of the virus. Tamiflu was discovered by Gilead scientists in 1996, and Gilead conducted all the initial characterization of the compound and developed the manufacturing process for the product.

Also in 1996, Gilead entered into an exclusive agreement with F. Hoffman-La Roche of Basel, Switzerland, providing for the development and commercialization of Tamiflu worldwide. According to the agreement's terms, Gilead and La Roche collaborated on Tamiflu's clinical development, with Gilead successfully managing three out of the four registrational trials leading to FDA approval. Since the U.S. product launch in late 1999, however, La Roche has been solely responsible at its own expense for product commercialization, including manufacturing, marketing, and distribution “in substantially all markets of the world.”

While vaccination is the primary weapon in combating influenza, we believe Tamiflu is a key component in addressing the potentially devastating impact of the disease. The role of Tamiflu must be better recognized, not just for pandemic planning, but also for seasonal influenza outbreaks. It bears emphasis that Tamiflu is not just effective for treatment of influenza, but also effective for influenza prophylactic, meaning it can prevent transmission of the virus.

Since at least 2001, we believe that our partner Roche has neither demonstrated acceptable commitment nor dedicated adequate resources to Tamiflu.
Chairman Tom Davis. Dr. Milligan, we are really not interested in the corporate disputes. If we could move on. We are really interested in your product, and the fact that you and Roche can work out your problems and make sure that we get this to market.

Dr. Milligan. I agree. At the heart of this, this is a commercial issue between the two companies, and not an action that we take lightly. I want to underscore an important point, which is that this action will not affect current arrangements or planning for the manufacture and supply of Tamiflu.

Roche is responsible, and will be responsible, for ongoing manufacturing, until time such time as the termination of the agreement becomes effective. The agreement also explicitly provides that in the event of termination, Roche must continue to supply product for up to 2 years and must transfer necessary manufacturing technology to Gilead.

Consequently, Gilead anticipates a coordinated and orderly process for the transfer of manufacturing, should termination occur. During any period of transition thereafter, Gilead will honor the supply obligations undertaken by Roche.

I would like to be especially clear about Gilead's commitment to advancing the care of patients suffering from diseases. In the mid and late-1990's, Gilead conducted extensive research on oral neuraminidase inhibitors, the class of drug to which Tamiflu belongs. We moved Tamiflu into clinical evaluation because, among the compounds we tested, it had the best potential safety and efficacy profile.

In accordance with our 1996 contract with Roche, Gilead continued to conduct extensive research into various compounds that showed activity against influenza A and B. Many structural classes were identified; however, none of these were thought to have better properties than Tamiflu, and none are currently being pursued as viable options for the treatment and prevention of influenza. Any of these compounds would be included in the 1996 agreement between Gilead and Roche, and Gilead would not be free to pursue any of these on its own.

I also want to highlight that Gilead is a leader in the manufacturing of antiviral medicines at large scales. Our expertise drawn from experience with HIV therapeutics is highly relevant to the situation surrounding the influenza pandemic. Gilead has and is continuing to manage the manufacturing of our HIV products in amounts that well exceed 2004 and anticipated 2005 production volumes for Tamiflu.

Comparable to the unpredictability of flu pandemics, the rapidly growing global HIV epidemic has required a carefully structured manufacturing plan for antiretrovirals, in absence of accurate forecasts estimating the number of patients to be treated for HIV resource-limited countries for years to come. Further, before issuing the notice of termination, Gilead conducted a thorough internal assessment of our capabilities. We determined that we can meet the global pandemic and seasonal needs for Tamiflu and make significant contributions in advancing manufacturing, supply, and medical education for this important antiviral medicine.

At Gilead, we believe that important lessons can be learned from previous annual influenza seasons, particularly with regard to the
administration of Tamiflu. If the effort is made to study the facts and data available to us, and to engage with leaders in global public health, these lessons can and should be applied to enhance responses to both seasonal and pandemic flu.

For instance, much attention has been drawn to the fact that in order to be most effective for combating influenza, Tamiflu must be taken within 48 hours of exposure to the virus. It is true that this 48-hour window is absolutely critical to ensure better outcomes for the infected individuals and the existence of this window highlights the importance of advancing education, securing supply, and breaking down the barriers to rapid access to the product. In order to underscore this crucial point, I have made available to the members of the committee a paper published by the Journal of Antimicrobial Chemotherapy on the benefits of early administration of Tamiflu.

Our role, should Tamiflu rights be returned to Gilead, will be one of planning and partnership. We believe there is an urgent need for increased education about and access to Tamiflu, not only for pandemic purposes, but as importantly for seasonal influenza.

Gilead looks forward to establishing partnerships with the distinguished committee members and government agency representatives here today, and with governments and public health officials around the world. We are prepared to enter into constructive dialog about the important role of Tamiflu in global public health, which we intend to fully support with appropriate, constructive action.

Thank you.

[The prepared statement of Mr. Milligan follows:]
Mr. Chairman, Congressman Waxman, Committee Members – thank you for the invitation to be here today. I am John Milligan, Executive Vice President and Chief Financial Officer of Gilead Sciences. By way of background, I am a PhD biochemist by training, and I was the project team leader for the development of Tamiflu® by Gilead.

About Gilead Sciences
Gilead is a biopharmaceutical company headquartered in Foster City, California – the district of Congressman Tom Lantos. We also have research facilities in Durham, North Carolina, a manufacturing facility in San Dimas, California, and overseas offices throughout Europe and Australia.

Since Gilead was founded nearly 20 years ago, the company has focused on advancing the care of patients suffering from life-threatening diseases. Over the course of our company’s history, Gilead has successfully developed, commercialized and ensured broad access to a portfolio of antiviral medicines in HIV and hepatitis. Today, these important antivirals are improving the quality of life for patients around the globe. Gilead does not achieve this alone, but through a strong commitment to collaboration – working in partnership within our industry, with governments, with health care professionals and with nongovernmental organizations.

Development of Tamiflu (oseltamivir phosphate) – Gilead’s Role
As you may know, Gilead is the inventor of Tamiflu, or oseltamivir phosphate. Tamiflu is the first and only antiviral pill available for the treatment and prevention of all common strains of influenza A and B. The compound has been shown to be active in animal models against avian flu, also known as the H5N1 strain of the virus. Tamiflu was discovered by Gilead scientists in 1996, and Gilead conducted all the initial characterization of the compound and developed the manufacturing process for the product.

Also in 1996, Gilead entered into an exclusive agreement with F. Hoffmann-La Roche of Basel, Switzerland, providing for the development and commercialization of Tamiflu worldwide. According to the agreement’s terms, Gilead and Roche collaborated on Tamiflu’s clinical development, with Gilead successfully managing three out of the four registration trials leading to FDA approval. Since the U.S. product launch in late 1999, however, Roche has been solely responsible, at its own expense, for product commercialization, including manufacturing, marketing and distribution “in substantially all markets of the world.”

While vaccination is the primary weapon in combating influenza, we believe Tamiflu is a key component in addressing the potentially devastating impact of the disease. The role of Tamiflu must be better recognized not just for pandemic planning, but also for seasonal influenza outbreaks. It bears emphasis that Tamiflu is not just effective as a treatment for influenza
patients, but is also an effective influenza prophylactic, meaning it can prevent transmission of the virus. Each year, influenza results in 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths worldwide. In the United States alone, up to 40 million Americans develop the flu, more than 200,000 people are hospitalized and 36,000 people die as a result of the flu and its complications during the average flu season.

Gilead’s Partnership with Roche – June 2005 Notice of Termination
Since at least 2001, we believe that our partner, Roche, has neither demonstrated acceptable commitment, nor dedicated adequate resources to Tamiflu. This has led to a lack of awareness of the product and its benefits by health care professionals.

On June 23, Gilead delivered to Roche a notice of termination for material breach of our 1996 Agreement. Gilead’s decision to terminate the agreement follows the communication of the company’s concerns over a period of several years — concerns communicated repeatedly, without results. We believe our decision to provide notice of termination of the 1996 Agreement is justified by the following material breaches: (1) Roche has failed to use best efforts to commercialize Tamiflu by adequately promoting and marketing the product in a sustained manner in all significant markets; and (2) Roche has failed to use best efforts to commercialize Tamiflu, evidenced by past problems with the manufacturing process that led to recalls and shortages in product supply; and (3) Roche has failed to pay all royalties fairly owed to Gilead.

At its heart, this is a commercial issue between two companies. This is not an action we take lightly. Our actions — and I want to underscore this important point — will not affect current arrangements or planning for the manufacture and supply of Tamiflu. Roche is responsible and will be responsible for ongoing manufacturing until such a time as the termination of our Agreement becomes effective. The Agreement also explicitly provides that, in the event of termination, Roche must continue to supply product for up to two years and must transfer necessary manufacturing technology to Gilead. Consequently, Gilead anticipates a coordinated and orderly process for the transfer of manufacturing, should termination occur. During any period of transition and thereafter, Gilead will honor the supply obligations undertaken by Roche.

I’d like to be especially clear about Gilead’s commitment to advancing the care of patients suffering from life-threatening infectious diseases. In the mid and late 1990s Gilead conducted extensive research on oral neuraminidase inhibitors – the class of drug to which Tamiflu belongs. We moved Tamiflu into clinical evaluation because among the compounds we tested, it had the best potential safety and efficacy profile. In accordance with our 1996 contract with Roche, Gilead has continued to conduct extensive research into various compounds that have shown activity against Influenza A and B. Many structural classes were identified, however, none of these were thought to have better properties than Tamiflu and none are currently being pursued as viable options for the treatment and prevention of influenza. Any of the compounds would be included in the 1996 agreement between Gilead and Roche, and Gilead would not be free to pursue these on its own.

Manufacturing Expertise
I want to also highlight that Gilead is a leader in the manufacture of antiviral medicines at large scales. Our expertise drawn from experience with HIV therapeutics is highly relevant to the situation surrounding a potential influenza pandemic. Gilead has and is continuing to manage the manufacturing of our HIV products in amounts that well exceed 2004 and anticipated 2005 production volumes for Tamiflu. Comparable to the unpredictability of flu pandemics, the rapidly growing global HIV epidemic has required a carefully structured manufacturing plan for
antiretrovirals, in absence of accurate forecasts estimating the number of patients to be treated for HIV in resource-limited countries in years to come. Further, before issuing the notice of termination, Gilead conducted a thorough internal assessment of our capabilities. We determined we can meet the global pandemic and seasonal needs for Tamiflu and make significant contributions in advancing manufacturing, supply and medical education for this important antiviral medicine.

Need for Ongoing Education
At Gilead, we believe that important lessons can be learned from previous annual influenza seasons – particularly with regards to the administration of Tamiflu. If the effort is made to study the facts and data available to us, and to engage with leaders in global public health, these lessons can and should be applied to enhance responses to both seasonal and pandemic flu events.

For instance, much attention has been drawn to the fact that, in order to be most effective for combating influenza, Tamiflu must be taken within 48 hours of exposure to the virus. It is true that this 48-hour window is absolutely critical to ensure better outcomes for the infected individuals and the existence of this window highlights the importance of advancing education, securing supply and breaking down barriers to rapid access to the product. In order to underscore this crucial point, I have made available to the Members of the Committee a paper published by the Journal of Antimicrobial Chemotherapy (accepted on September 24, 2002) on the benefits of early administration of Tamiflu.

Gilead’s Commitment to Partnership
Our role, should rights to Tamiflu be returned to Gilead, will be one of planning and partnership. We believe that there is an urgent need for increased education about and access to Tamiflu – not only for pandemic planning purposes, but as importantly for seasonal influenza.

Gilead looks forward to establishing partnerships with the distinguished committee members and government agency representatives here today, and with governments and public health officials around the world. We are prepared to enter into constructive dialogue about the important role of Tamiflu in global public health, which we intend to fully support with appropriate, constructive action. Thank you.
Early administration of oral oseltamivir increases the benefits of influenza treatment

F. Y. Aoki†1, M. D. Macleod1, P. Paggiaro1, O. Carewicz1, A. El Sawy1, C. Wart1, M. Griffiths6, E. Wallberg2 and P. Ward6 on behalf of the IMPACT Study Group†

1University of Manitoba, Room 510–730 William Avenue, Winnipeg, Canada; 2Aldershot Health Centre, Aldershot; 3Roche Global Development, Welwyn, U.K.; 4Cardiothoracic Department, Cirillo Hospital, Pisa, Italy; 5Dusseldorf, Germany; 6University of the Alps, Saint Martin d’Heres, France; 7Roche–La Roche, Basel, Switzerland

Received 4 January 2002; returned 10 April 2002; revised 3 July 2002; accepted 24 September 2002

Our objective was to evaluate the benefit of early treatment of influenza illness using oral oseltamivir. This open-label, multicentre international study investigated the relationship between the interval from illness onset to first dose (time-to-treatment) and illness duration in the intent-to-treat infected population using accelerated failure time (AFT) modelling. A total of 1,426 patients (12–70 years) presenting within 48 h of the onset of influenza symptoms were treated with oseltamivir 75 mg twice a day for 5 days during the 1999–2000 influenza season; 958 (67%) had laboratory-confirmed influenza virus infection. Earlier intervention was associated with shorter illness duration (P = 0.0001). Initiation of therapy within the first 12 h after fever onset reduced the total median illness duration by 74.6 h (2.1 days; 41%) more than intervention at 48 h. Intermediate interventions reduced the illness proportionally compared with 48 h. In addition, the earlier administration of oseltamivir further reduced the duration of fever, severity of symptoms and the time to return to baseline activity and health scores. Oseltamivir was well tolerated. The most common adverse events were nausea and vomiting, which were transient and generally occurred only with first dosing. When oseltamivir was taken with food, the tolerability was enhanced. The overall discontinuation rate was low (1.8%). In conclusion, the IMPACT study demonstrated that earlier initiation of oral oseltamivir therapy increased its therapeutic effects, which were seen at every time point of intervention and were progressive. Thus, early presentation, diagnosis and treatment of patients with influenza maximized the benefits of oseltamivir therapy.

Keywords: influenza, neuraminidase inhibitors, oseltamivir, treatment

Introduction

Annual influenza outbreaks lasting for 6–8 weeks result in illness in an average of 10% of the population.1 Influenza disrupts the normal activities of individuals and, because of the large number of people incapacitated by the illness, results in a considerable burden to society.2,3 Increases of up to five-fold in consultations for influenza-like illness in general practice intensifies pressure on primary healthcare services.4 There is a need for effective and well-tolerated treatments that can reduce the impact of influenza on the individual and society. Oseltamivir is the oral produg of oseltamivir carboxylate, a potent inhibitor of influenza A and B viral neuraminidase. Oseltamivir is well tolerated and effective for the treatment of acute influenza in previously healthy adults.5,6 In influenza-infected patients treated within 36 h of symptom onset, oseltamivir reduced the duration of clinical illness by 50% (P < 0.001), when compared with symptomatic treatment alone.7

The pathogenesis of influenza illness suggests that inhibiting viral replication as early as possible after infection will reduce the duration and intensity of symptoms. In the study of

*Corresponding author. Tel: +1-204-789-5525; Fax: +1-204-789-3236; E-mail: netensn@umanitoba.ca
†Members of the IMPACT Study Group are listed in the Acknowledgements.
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Nicholson et al.3 patients starting oseltamivir within 24 h of symptom onset had a 37% reduction in illness duration compared with placebo. Studies with the inhaled influenza neuraminidase inhibitor zanamivir have also suggested the additional benefit of earlier treatment.19 These findings are consistent with increased treatment benefits that result from early antiviral treatment of other viral diseases.38

The IMPACT (Immediate Possibility to A/Cease Oseltamivir) Treatment) study investigated the relationship between the time to intervention and duration of illness as a primary end-point, plus other parameters of illness, by treating with oral oseltamivir as early as possible after the onset of influenza symptoms.

Materials and methods

This was a prospective, open-label, exploratory, multicentre international study conducted during the influenza season 1999–2000. During local influenza outbreaks, subjects aged ≥13–70 years presenting within 48 h of the sudden onset of fever (≥37.8°C, ≥100°F) with at least two of the following symptoms: cough, sore throat, coryza, myalgia, headache, fatigue and chilliness/sweats were enrolled and received oral oseltamivir 75 mg twice a day for 5 days. Volunteers were advised to take the study medication with a meal or snack, and ingestion of the first dose was observed directly and the time recorded. Those with uncontrolled chronic medical disorders were excluded as were women who were pregnant, lactating or not using a reliable method of contraception. Individuals who had HIV infection, a transplant or a clinically relevant history of abuse of alcohol or other drugs were excluded. Subjects who had experienced an acute upper respiratory tract infection (URTI), otitis media, bronchitis or sinusitis or who had been treated with an antiviral drug, systemic steroids or immunosuppressants within 2 weeks of the study start were also excluded. Influenza infection was confirmed by virus recovery from nose or throat swabs taken pre-dose and on day 3 (in selected centres only), and/or a 2-fold increase in serum antibody titre to influenza virus. Nose and throat swabs were transported to country-specific virology laboratories either in chilled viral transport medium within 72 h or in ambient conditions within 24 h of collection from the patient. The swabs were eluted and inoculated onto Madin-Darby canine kidney (MDCK) cell monolayers and incubated for 7 days. Cell-associated influenza A or B viruses were identified using immunofluorescence antibody techniques or the haemadsorption test.

Baseline and day 21 sera were assayed together by measurement of the haemagglutination-inhibition (HAI) antibody or complement fixation test (CFT) antibody. The following antigens were used for the majority of HAI assays: A/Bayern/795 (H1N1), A/Sydney/597 (H3N2), B/Yamagata/166/98; the antigens used for CFTs were influenza A and B nucleocapsid.

Temperature and symptom scores were recorded twice daily and a health scale questionnaire was answered daily for 21 days after the start of the study.

The primary endpoint was duration of illness as a function of time to the first treatment dose, calculated from the time of onset of fever (defined as the earliest time that the patient either measured an elevated temperature or felt feverish) in the laboratory-confirmed influenza virus-infected population. The duration of illness was defined as the time from symptom onset to alleviation of all symptoms. Duration of illness was measured from the onset of fever or when the patient felt feverish until all symptoms were scored as mild or absent and remained so for at least 24 h. Other endpoints included the severity of the influenza illness by measurement of area under the curve of total symptom scores, the times to resolution of fever (assessed as the time to return to an afebrile state, i.e. a temperature of ≤37.2°C), and return to baseline health and activity scores. Adverse events were recorded up to study day 21 (±4) and graded on a four-point scale (mild, moderate, severe, life-threatening).

The study was conducted in accordance with the principles of the Declaration of Helsinki (Amended) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The protocols were approved by local ethical committees prior to implementation and all participants gave written informed consent before enrolment.

Analysis of data

To determine the added value of early intervention, the relationship between time to treatment and illness duration from fever onset was analysed. The results were compared descriptively by time-to-treatment groups and also by accelerated failure time (AFT) modelling on the actual data collected.14

The LIFEREG procedure in SAS (version 6.12) was used to perform the AFT analysis, in a Unix environment. Estimates were produced on the natural log scale, but were back-transformed for presentation in all summary tables. The error structure was modelled using the log-normal distribution, and for all best fit models, normal probability plots of the residuals were produced and examined for indications of lack-of-fit.

The median times of illness duration from illness onset are also presented for time-to-treatment groups together with 95% confidence intervals.

Kaplan–Meier curves of the duration of illness data were constructed for each time-to-treatment group in order to estimate the median duration of illness and associated 95% confidence interval along with other summary statistics.
Early treatment benefits of oseltamivir

Table 1. Summary of the demographics of the safety population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Oseltamivir 75 mg twice a day (n = 1426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>716 (50%)</td>
</tr>
<tr>
<td>Median age (range; years)</td>
<td>40.0 (12-70)</td>
</tr>
<tr>
<td>Influenza virus infected, n (%)</td>
<td>958 (67%)</td>
</tr>
<tr>
<td>type A</td>
<td>944 (66%)</td>
</tr>
<tr>
<td>type B</td>
<td>6 (0%)</td>
</tr>
<tr>
<td>type A and B</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>unknown</td>
<td>25 (2%)</td>
</tr>
<tr>
<td>Influenza vaccinated, n (%)</td>
<td>121 (8%)</td>
</tr>
</tbody>
</table>

Results

A total of 1428 patients entered the study. Of these, 1426 received study treatment and comprise the intent-to-treat (ITT) safety population (Table 1). Two 12-year-old patients, who deviated from the age inclusion criteria, were included in the ITT population. The intent-to-treat infected (ITTI) population consisted of the 958 (67%) subjects with laboratory-confirmed influenza, 955 of whom received study medication and provided data permitting calculation of the clinical endpoints. There were no major differences in infection rates between the time windows. Of the ITTI population, 140 (15%) subjects entered the study within 6 h of symptom onset, 240 (25%) within the first 12 h and 573 (60%) within 24 h. There was a correlation between the time of intervention after symptom onset and the illness duration, such that the duration of illness was shorter the earlier treatment began (Table 2). AFT modelling of the data confirmed that earlier intervention was strongly associated with shorter illness duration ($P < 0.0001$) (Table 3 and Figure 1). Intervention within the first 12 h after fever onset reduced the median illness duration by 3.1 days more than if intervention was delayed until 48 h (Figure 2). For every 6 h earlier that oseltamivir was initiated, the predicted median illness duration was shortened by an acceleration factor of 1.09 (95%). This corresponded to a benefit of $-1.0$ h (range $-1.15$) shorter duration of illness for every 6 h earlier that treatment was initiated. The outcomes based on the absolute time-to-treatment group data and those produced by the use of AFT modelling results were highly comparable.

As well as the additional benefit of early administration on illness duration, benefits were also seen in other efficacy endpoints. Earlier intervention was strongly associated with a shorter time to return to normal health ($P = 0.0001$) and baseline activity ($P = 0.0001$) (Figure 3). Earlier intervention also reduced the fever duration ($P = 0.0315$) (Figure 4) and severity of illness ($P = 0.0023$) (Figure 3). The acceleration factors for these parameters were 1.05, 1.07, 1.12 and 1.03, respectively. Approximately 99% of all influenza-infected

Table 2. Duration of illness observed in the intent-to-treat infected population (n = 955) per time-to-treatment group in patients treated with oseltamivir 75 mg twice daily for 5 days

<table>
<thead>
<tr>
<th>Duration of illness (h) between onset of symptoms and treatment start</th>
<th>0-6 (n = 140)</th>
<th>&gt;6-12 (n = 100)</th>
<th>&gt;12-24 (n = 332)</th>
<th>&gt;24-36 (n = 258)</th>
<th>&gt;36-48 (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration (h)* (95% CI)</td>
<td>81.8 (70.7-105.5)</td>
<td>110.2 (93.0-123.5)</td>
<td>112.1 (98.5-122)</td>
<td>127.8 (111.8-151.5)</td>
<td>180.0 (146.7-202.8)</td>
</tr>
</tbody>
</table>

*The time from the start of the illness to alleviation of all symptoms.

Table 3. Duration of illness predicted by the AFT model* in patients treated with oseltamivir 75 mg twice daily for 5 days

<table>
<thead>
<tr>
<th>Time (h) from start of illness to treatment</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted median illness duration (h)</td>
<td>90.7</td>
<td>98.9</td>
<td>108</td>
<td>128.7</td>
<td>153.3</td>
<td>182.6</td>
</tr>
<tr>
<td>Reduction in illness duration (h)* (95% CI)</td>
<td>91.9</td>
<td>83.6</td>
<td>74.6</td>
<td>53.9</td>
<td>29.3</td>
<td>NA</td>
</tr>
<tr>
<td>(78.4-107.7) (72.2-96.8) (65.9-85.6) (47.2-61.5) (25.3-33.9)</td>
<td>2.01</td>
<td>1.85</td>
<td>1.69</td>
<td>1.42</td>
<td>1.19</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Model covariates are age, baseline total symptoms score, vaccination status time-to-treatment, baseline total symptom score time-to-treatment interaction.

NA, not applicable; CI, confidence interval.
patients treated with oseltamivir had a reduction of fever, <37.8°C, within 36 h of taking their first dose.

The duration of illness was seemingly shorter when intervention occurred earlier in patients who were not infected with influenza and treated with oseltamivir, but this was not statistically significant (P = 0.3783) (Table 4). Thus, no therapeutic benefit was demonstrable as a result of oseltamivir treatment in non-influenza virus-infected patients.

Oseltamivir was well tolerated. The incidence of adverse event-related drug withdrawal was low, 25/1426 (1.8%), and was similar to the number of patients who withdrew for reasons related to adverse events (n = 21/1426, 1.5%). Most adverse events were mild or moderate in severity. The most common adverse events were gastrointestinal, mainly nausea (194/1426, 13.6%) and vomiting (160/1426, 11.2%), which resolved with continued dosing; only 12 subjects (<1%) withdrew as a consequence of these effects. The majority of these events occurred between the first and second dose (<7%). The incidence of nausea was further reduced when the first dose was taken with food (6.6%) compared with no food (13.6%, P = 0.026).

The overall incidence of vomiting was higher in patients with influenza infection (9.9%) than in those without (6.6%, P = 0.012).

Discussion

The IMPACT study, designed to investigate the relationship of time-to-treatment with the illness duration and other efficacy parameters, has confirmed that greater and incremental benefits can be gained from treating influenza as soon as possible after the appearance of symptoms. The study design was predicated on knowledge that influenza illness is associated with virus replication in the respiratory tract that peaks 24–72 h after illness onset. Thus, drugs like oseltamivir that would ameliorate illness solely by inhibiting virus replication must be administered in the first 48–72 h of illness, and preferably as early as possible. Early intervention was shown to be strongly associated with a shorter duration and a reduced severity of illness, a faster resolution of fever and a faster return to normal health and activity. For the primary endpoint, the data demonstrated that the total duration of illness could be halved if influenza patients were treated early compared with intervention at 48 h. These data complement the results from an earlier study with oseltamivir in which subjects who started active treatment within 24 h of
symptom onset had a 37% reduction in illness duration compared with 25% in those who initiated therapy within 36 h after onset of illness. This is the first report to describe the mathematical relationship between illness duration and time to effective antiviral intervention. The results based on the observed time-to-treatment group data and those produced by AFT modelling were highly comparable. The time-to-treatment group data consisted of results for all subjects recruited within specified mean 6 or 12 h windows, whereas AFT modelling permitted us to predict the effect of intervention at any time as well as the results of extrapolation to the limits of time studied. The observed effects and the values predicted by AFT modelling were somewhat different even though they were both derived from analysis of the study database.

The absence of a concurrent control group treated with placebo in this study might raise the question of whether the beneficial effects of early initiation of oseltamivir plus symptomatic therapy in persons with influenza illness were due to early initiation of symptomatic therapy alone. This is unlikely given the previous observation in persons with laboratory-confirmed influenza who were treated with the same symptomatic therapy plus placebo, in whom no difference was observed in the median duration of illness between those persons treated at <36 h and those in whom therapy was initiated within 24 h of illness onset. The study confirmed that physicians can accurately diagnose influenza in patients reporting soon after fever onset by use of a clinical case definition and knowledge that influenza virus is circulating within the community. There were no major differences in the sensitivity of the clinical diagnosis between the treatment time windows, and the 67% infection rate was similar to that found in previous placebo-controlled treatment studies with oseltamivir. The study also confirmed that influenza presents with characteristic sudden identifiable and severe symptom onset, 92 only 2/958 patients having presented with mild symptoms in this study. Education of potential volunteers about symptoms of influenza illness made possible self-referral for diagnosis and the implementation of antiviral therapy. The proportion of individuals with influenza who receive some form of drug treatment is 59%. Antibiotics are the most frequently prescribed drugs (45%), followed by antipyretics/analgesics (22%). Antibiotics are largely prescribed to patients with influenza in all age groups. Inappropriate antibiotic treatment provides no medical benefit and increases the risk of antibacterial resistance. The results of this study confirm that oseltamivir therapy would be more logical than antibiotics for patients with uncomplicated influenza.

Translating the results of this study into clinical practice will be challenging, but, it is argued, clinically important. Strategies to do so must provide early diagnosis and access to oseltamivir therapy without markedly increasing the workload for practitioners in the influenza season. This study has demonstrated that early presentation is possible by public education of influenza symptom characteristics, as approximately two-thirds of those who were infected presented to their general practitioners within 24 h of symptom onset, and a quarter within 12 h. One solution may be in application of the UK Department of Health guidelines to implement the NICE recommendations for another neuraminidase inhibitor drug, zanamivir. Telephone triage and walk-in centres for specific patient groups organized by practice nurses or other health professionals, e.g. community pharmacists, working to a protocol of standard diagnostic questions will help address the issues of overburdened GPs and facilitate timely initiation of treatment.

The overall incidence and pattern of adverse events were similar to those reported in previous studies. Nausea was significantly reduced by taking the first dose of oseltamivir with food, suggesting that the mechanism of action may be at the local gastric level. The proportion of patients who discontinued drug because of gastrointestinal events was small and similar to previous studies, due to the fact that the majority of these events were of isolated occurrence after the first dose and did not persist with continued dosing.

Conclusion

The IMPACT study adds to our understanding of the benefits of oral oseltamivir therapy of influenza, by demonstrating that earlier intervention enhances treatment effects. Early intervention can reduce the total illness duration by up to one
half compared with later treatment, resulting in faster recovery and resumption of normal activities. The IMPACT study demonstrated the value of early presentation and diagnosis of patients with influenza illness and their treatment with oseltamivir.

Acknowledgements

We thank all participating physicians, study investigators and the Roche study management team (Charlotte Harding Rasm, Penny Kittywood, Kevin Drabble, David Merrett, Laurence Bourdeau, Diane Gillis and Shelina Rajan) who made this project possible. The authors gratefully acknowledge Stephen Pawsey (clinical science), Jennifer Gilbide, Nelson Kinney, Tracy Mills and Paul Mahoney (biostatistics) at Roche Global Development. We would also like to acknowledge the contribution of Dr Torsten Hoo who helped with the design of this study. This study was financially supported by F.Hoffman-La Roche Ltd.

Study investigators: Belgium: Didier, Vanret – Namur; Frans, Pardiniez – Antwerp; Didier, Giet – Liege; Bernard, Clarisse – West-Vlaanderen; Jacques, Sintgo – Hainaut; Frank, Decorte – Limburg; Rodolphe, Liage – Ost-Vlaanderen; Noel, Provoost – Vlaams Brabant; Canada: Dr G. Aseyan – Regina; Dr Marc Afflato – Montreal; Dr Gordon Aube – Toronto; Dr Laurie Berger – Montreal; Dr L. Campbell – Montreal; Dr David Carswell – Harrow; Dr Howard Carter – Halifax; Dr Percy Crocker – St John’s; Dr Francisco Diaz-Mitmon – Ottawa; Dr Anthony D’Orta – Toronto; Dr G.W. Hammond – Winnipeg; Dr Brian K. Holoway – Edmonton; Dr Allan Kelley – Edmonton; Dr Gerald Lazarek – Calgary; Dr P.H. Orr – Winnipeg; Dr Jean-Pascal Ouellet – Sherbrooke; Dr Flynn Patel – Toronto; Dr Daniel Shu – Vancouver; Dr J.N. Simonsen – Winnipeg; Dr Gay Silver – Montreal; Dr Sylvie Trutier – Quebec City; Dr Paul Whaitie – Oshawa; Denmark: Bente, Kuhlen – Copenhagen; Ronald, Dahl – Aarhus; Jacobson – Vige; Layboone – Copenhagen; Schelde – Vig; Witsenup – Soro; Perti, Himsen – Turku; Timo, Kaiutti – Lappeenranta; Leena, Kittel – Koojo; Perti, Kivi – Tamper; Jane, Koski – Jyvaskyja; Merja, Pittakas – Helsinki; Arto, Strandberg – Helsinki; Timo, Venkari – Tamper; France: Dr Alain Caigne – Tours; Dr Gilles Grandmoulin – Besancon; Dr Michel Gregoire – Taille; Dr Dominique Lejay – Verst Combe; Dr Charles Mercier – Hes: Montaigne; Dr Gerald Mengin – Mont Pelletier; Dr Simon Musso – Eauze; Dr Francois Sphiteeron – Evreux; Dr Richard Josse – Berne; Dr Bruno Pasca – Toulon; Dr Jean-Looy Roy – Armees; Dr Jean-Louis Soares – Armees; Germany: Dr Flob- dorf – Duren; Dr Bagdos – Dormage; Dr Gesert – Rothenburg; Dr Schlue – Loeben; Dr Adler – Ludwigshafen; Dr Lukie – Freiberg; Iceland: Gunnar, B. Gunnarsson – Reykjavik; Vilhjalmur, Arn Arason – Hofafjordur; Jon, Stener Jonsson – Gardabaer; Ireland: Dr Tom Finnegan – Dublin; Dr Brian O’Doherty – Droghane; Dr Niall Moore – Dublin; Dr Liam Lynch – Dublin; Dr Philip O’Connell – Dublin; Dr Alan Byrne – Dublin; Dr William Kavanagh – Dublin; Dr Tim Gleeson – Dublin; Israel: Prof Shai Askenazi – Petach-Tikva; Dr Efrat Harlev – Sharon; Prof Ethan Robinson – Givatazem; Dr Aya Shemesh – Hadera; Dr Tessa Sheleuchte – Hadera; Dr Dorit Wolf – Natania; Dr Moshe Zlotnik – Askelu; Dr Bibiana Chazan – Tiberias; Dr Bassa – Ofakim; Dr David Hassin – Hadera; Dr Nir Hele- zen – Kfar-Saba; Dr Ronan Hemomi – Hadera; Dr Liora Ben, Netzar Marika – Petach Tikva; Dr Raul Katz – Afula; Dr Moshe Tisser – Afula; Dr Tsvika Weiss – Herzliya; Dr Yoan Menda – Herzliya; Dr Akram Abdell – Ofakim; Dr Bibiana Chazan – Tiberias; Dr Gay Nir – Afula; Dr Avraham Bezer – Ofakim; Dr Bar-Sheva Gutterman – Kfar-Saba; Dr Yova Helman – Natania; Dr Oma Ofir – Afula; Prof Francis Schlafler – Beer-Sheva A; Dr David Gabay – Rishon Lezion; Dr Oran Avraham – Natania; Dr Cuna Sullivan – Tiberias; Italy: Prof Pierre Cournu – Genova; Netherlands: Dr G.J.M. Van Deuren – Lichtenvoorde; Luiten – Den Haag; Dr R.G.G. Groen – Amstelden; Dr P.H.L. Hofstede – Giekenh; Dr F.B.R. Naber – Hornmeker; Dr J. Veerman – Nijverd; Norway: Sigbjorn – Elle – Eilerum; Mikkel, Mundal – Oslo; Niels-Erik, Lindmark – Sandvika; Sjur-Ro-Larsen – Asgard- strand; Pal, Vak – Sandvika; Kristian, Furuhe – Jessheim; Signe, Tonstad – Oslo; Age, Bjerntaus – Trondheim; Sweden: Dr Gun-Cronberg – Malmoe; Dr Per Forsberg – Vaxjo; Dr Peter Hogstensen – Karlskrona; Dr Bo Claesson – Goteborg; Dr Mikael Valfrid – Sandefjord; Dr Eva Gold – Helsingby; Switzerland: Claude, Breitenstein – Liestal; Roland, Selt – Margrethen; Urs, Beat Geffin – Binningen; Thomaso, Andreas – Lausanne; Eric, Jenson – Bern; Bisel, Georges – Lausanne; UK: Hall, Tim – Plymouth; Middleton – Fowey; Richde – Peterhead; Haworth – Blackpool; Dotel – Cleveleys; Newby – Cambridge; Rogers, D. – Edgbaston; Wallace, P. – Chandlers, Anderson, D. – Bristol; Crawford, A. – Winchester; Dove, N. – Harrow; Lynch, H. – Bolton; Fissay, M. – Roehde; Gilibalter, B. – Wrexham; Avena, S.B. – London; Jones, G. – Canterbury; Mossley, D. – Sheffield; Muir, W. – Nottingham; Quinn, Leslie – Glasgow; Richardson, D. – Dorset.

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Chairman Tom Davis. Thank you. Thank you very much.
Mr. Abercrombie.

STATEMENT OF GEORGE B. ABERCROMBIE

Mr. Abercrombie. Good morning. Good morning, Mr. Chairman and members of the committee. I am George Abercrombie, president and chief executive officer of Hoffman-La Roche, a research-based pharmaceutical company. I am accompanied today by Dr. Dominick Iacuzio, our medical director for Tamiflu. I want to thank you for the opportunity to discuss the role of Roche and the antiviral drug Tamiflu in pandemic influenza preparedness and response, and I request that my full written testimony be submitted for the record.

Chairman Tom Davis. Without objection, everybody's full written testimony is in the record.

Mr. Abercrombie. Since Roche licensed Tamiflu nearly 10 years ago, we have acted in a responsible manner, consistent with the public health role of this wonderful product and our commercial obligations. Roche remains committed to ensuring the availability of Tamiflu to patients and governments around the world, and we are optimistic that this unfortunate matter with Gilead will be resolved.

Let me now turn to the central office of this hearing, and that pandemic influenza, which is one of our greatest public health threats.

According to the Department of Homeland Security, the potential consequences of even a limited influenza pandemic could result in economic disruption, hospitalizations and deaths far in excess of most terror attacks. It is widely recognized that Tamiflu is critical and a critical tool in pandemic influenza preparedness. The Infectious Diseases Society of America has recommended that the U.S. stockpiles enough antivirals to treat up to 50 percent of the population.

Based on Roche's commitment to the product, Tamiflu is the leading prescription antiviral medication for the treatment of influenza type A and B in patients 1 year and older, and prevention of influenza type A and B in patients 13 and older. Data to support prophylactic use in children 1 year of age and older were recently submitted to FDA for review.

The efficacy of Tamiflu against avian influenza has been demonstrated by leading researchers and animal studies and in vitro data, and is supported by practical experience during a 2003 avian influenza outbreak in the Netherlands. In contrast to an antiviral drug requiring inhalation, orally ingested Tamiflu has been shown to be systemically active in humans. This is important because evidence derived from infected humans and animals suggests significant systemic involvement of the H5N1 avian virus.

Although the potential for resistance must be monitored carefully, no transmission of a Tamiflu-resistant virus in humans has been detected to date. Accordingly, the World Health Organization has recommended the use of Tamiflu to help control the avian flu outbreaks in Asia.

Roche continues to work closely with public health officials, physicians, and other healthcare professionals around the world in a
manner that is responsible and complimentary to seasonal flu vaccination programs. We have recommended against, and do not advocate for, indiscriminate uses which could lead to resistance, such as the prophylactic veterinary use of amantadine, recently reported in Asia.

Given inherent complexities in Tamiflu production, surge capacity to meet immediate, large-scale demand upon the outbreak of a pandemic, simply does not and cannot exist. The manufacturing process for Tamiflu takes 8 to 12 months from raw materials to finished product. The process involves many inputs and steps, including a unique starting material and a potentially explosive production step that can be carried out only in specialized and very costly facilities. Despite these limitations, since 2003, we are increasing total Tamiflu production capacity nearly eight-fold.

At the request of the U.S. Government, Roche has developed a new U.S.-based supply chain that will be launched in the third quarter of this year. Further, we have developed special U.S. packaging for stockpiled Tamiflu to extend the shelf life and ease distribution and administration. In addition, Roche has also discovered and developed a synthetic process for manufacturing the chemical used in the initial production step. This will ultimately reduce reliance on natural sources.

Roche has received and is filling on schedule pandemic stockpile orders for Tamiflu from 25 countries, and we have received letters of intent from five additional governments. Countries such as the United Kingdom, France, Finland, Norway, Switzerland, and New Zealand are ordering enough Tamiflu to cover between 20 and 40 percent of their populations. And just this morning the country of Portugal announced an order for 25 percent of their population.

Although discussions are underway with the U.S. Government to purchase significantly greater amounts of Tamiflu, achieving domestic stockpile levels comparable to other nations will require firm, sustained commitments from the U.S. Government.

If I can leave you with three messages, they are the following: first, there is a consensus by global health authorities that Tamiflu is an important tool in pandemic influenza preparedness and response; second, other nations are currently well ahead of the United States in Tamiflu stockpiling. We urge the United States to make expanded commitments now and over time to ensure an adequate Tamiflu stockpile.

Finally, I want you to know, Mr. Chairman and this committee, that the availability of Tamiflu as a part of a robust pandemic response remains my top priority as chief executive officer of Hoffman-La Roche.

On behalf of Roche, thank you for highlighting this critical public health issue. And Dr. Iacuzio and I will be pleased to answer any questions you may have.

[The prepared statement of Mr. Abercrombie follows:]
STATEMENT OF GEORGE B. ABERCROMBIE
PRESIDENT AND CHIEF EXECUTIVE OFFICER, HOFFMANN-LA ROCHE INC
BEFORE THE
COMMITTEE ON GOVERNMENT REFORM
UNITED STATES HOUSE OF REPRESENTATIVES

THE NEXT FLU PANDEMIC: EVALUATING U.S. READINESS

JUNE 30, 2005

Mr. Chairman and Members of the Committee, I am George Abercrombie, President and Chief Executive Officer at Hoffmann-La Roche Inc. ("Roche"), a research-based pharmaceutical company. I am grateful for this opportunity to discuss with you the roles of Roche and antiviral drugs in pandemic influenza preparedness and response, and I commend the Committee for its efforts to protect the American people against this very real public health threat.

THE PANDEMIC INFLUENZA THREAT

Every year, seasonal influenza causes an average of 36,000 deaths and 200,000 hospitalizations.\(^1\) In addition to the annual influenza seasons, three influenza pandemics took place during the 20th century. In 1918, approximately 500,000 people in the United States died from the so-called “Spanish Flu,” and up to 50 million may have died worldwide. The 1957-58 “Asian flu” killed 70,000 Americans, and the 1968-69 “Hong Kong flu” caused over 34,000 deaths in this country.\(^2\)

An influenza pandemic occurs when an existing influenza strain mutates. The emergence of such a new viral strain, the lack of previous exposure and immunity to the virus, and the lack of a

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\(^1\) William W. Thompson et al., Influenza-Associated Hospitalizations in the United States, 292 JAMA 1333 (2004).

\(^2\) Centers for Disease Control and Prevention, Fact Sheet: Information About Influenza Pandemics (March 8, 2005).
vaccine that can protect against the new strain can ignite a global influenza epidemic, i.e., a pandemic.

It now appears that the factors associated with a pandemic are moving into place. First, we have a highly pathogenic strain of avian influenza circulating widely in Asia. Second, this avian strain appears to be increasingly capable of causing deadly disease in humans and animals. In fact, the avian virus has been fatal in approximately 50 percent of people infected by it. While efficient human-to-human transmission of the virus – the critical barrier to an influenza pandemic – has yet to occur, it is possible – if not probable – that persons harboring both human and avian influenza viruses could become “mixing vessels” from which a new virus emerges that is easily transmitted among humans. Indeed, a recent World Health Organization (WHO) assessment noted that new epidemiological findings in Asia indicate that the virus may be becoming more capable of human-to-human transmission.4

Make no mistake: should an influenza pandemic occur, the threat to the U.S. public would be great. In its draft Pandemic Influenza Preparedness and Response Plan (Plan), the U.S. Department of Health and Human Services (HHS) recognizes an influenza pandemic as having “a greater potential to cause rapid increases in death and illness than virtually any other natural health threat.”5 Health experts estimate that if the virus is passed efficiently between humans, avian flu could result in a pandemic causing over 50 million deaths worldwide.6 Studies cited recently by the Centers for

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4 World Health Organization, Inter-country Consultation, Influenza A/H5N1 in Humans in Asia (May 6-7, 2005).


Disease Control and Prevention (CDC) estimate that, without vaccines or drugs, a “medium level” pandemic would kill between 89,000 and 207,000 Americans, and sicken another 20 to 47 million — causing up to 42 million outpatient visits and 734,000 hospitalizations. In fact, according to the Department of Homeland Security, the potential consequences of even a limited influenza pandemic could result in deaths, hospitalizations and economic disruption far in excess of most terrorist attack scenarios. In addition to the human toll, the economic cost of such a pandemic has been estimated at $71 to $167 billion. Without a doubt, planning for such a global health crisis must be a major public health priority.

Both the HHS draft Plan and the WHO Global Influenza Preparedness Plan emphasize that adequately addressing the threat of a pandemic influenza outbreak will require availability of both an influenza vaccine and antiviral drugs. If available, vaccines, which typically are administered before an outbreak of influenza, can provide an effective defense against developing seasonal or pandemic influenza, as well as in slowing transmission among humans.

In our seasonal marketing of Tamiflu®, we have carefully calibrated our messages and activities so they are complementary to, and do not undermine, efforts to promote broad seasonal vaccination for influenza. However, vaccines have important limitations, particularly in the pandemic influenza context. First, accurately predicting the specific viral strain or strains that ultimately may cause an influenza pandemic cannot be assured. Consequently, effective vaccines

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9 CDC, Influenza Pandemic Fact Sheet.

may not be available at the time a pandemic outbreak is first detected. Second, the propensity of viruses to mutate can lead to the rapid generation of new strains. Thus, there is a possibility that a vaccine effective against the viral strain accountable for the outbreak may be impotent against the virus' mutated progeny. This is one reason why unique vaccines to guard against seasonal influenza must be produced, licensed, and distributed each year, and thus, cannot be stockpiled for use against multiple outbreaks. Finally, given the pace of an outbreak of pandemic influenza, initial reliance on vaccines may not be feasible. For example, the WHO estimates it will take six to nine months to develop a vaccine effective against the circulating pandemic virus strain.\textsuperscript{11} Of course, producing and distributing the vaccine on a large scale also will take considerable time, and a vaccine, once administered, may take several weeks to trigger immunity, or require multiple administrations.

For all of these reasons, HHS and WHO have recommended that efforts to prepare for an influenza pandemic not rely on vaccines alone. As stated in a recent WHO report, "pending the availability of vaccines, antiviral agents will be the principal medical intervention for reducing morbidity and mortality, which becomes the most important priority once a pandemic is underway."\textsuperscript{12} Notably, certain antiviral drugs can be used either to treat the flu or as a prophylactic to prevent those at risk from becoming infected. Recently published models suggest that an influenza pandemic could be contained if 80 percent of those exposed to the virus used targeted antiviral drugs prophylactically.\textsuperscript{13}


Finally, antivirals have four additional characteristics that warrant their inclusion in any influenza pandemic plan: (1) antivirals have a long shelf-life – five years in the case of Tamiflu® capsules – permitting them to be stockpiled and immediately available when an outbreak occurs; (2) antiviral drugs begin to work immediately after they are administered; (3) certain antivirals work against multiple types of influenza; and (4) utilization of antivirals does not interfere with immunologic response, meaning that patients can still develop immunity to the virus while taking Tamiflu® to protect them.

**THE ROLE OF TAMIFLU® IN AN INFLUENZA PANDEMIC**

Roche’s Tamiflu® (oseltamivir phosphate) is the leading prescription oral antiviral drug for influenza. Roche licensed the product from Gilead Sciences, and accelerated development of the product through Phase II and III studies, as well as the Food and Drug Administration (FDA) approval process. Recently, Gilead Sciences sent to Roche a notice seeking to revoke the license for Tamiflu®. We at Roche are deeply disappointed by Gilead’s actions, and strongly disagree with their public statements regarding Roche’s Tamiflu®-related efforts. However, we are also optimistic that the dispute will be resolved, and committed to ensuring this matter does not disrupt or delay the production and subsequent availability of Tamiflu®, or impinge upon supply commitments made to governments around the world.

Tamiflu® was first approved by the FDA in 1999 for the treatment of adults with type A and B influenza. Specifically, Tamiflu®, a neuraminidase inhibitor, works by attacking the influenza virus and its ability to replicate, rather than simply addressing influenza symptoms. Currently, Tamiflu® is indicated for treatment of patients one year and older, and, if taken within forty-eight hours of the onset of symptoms, can help patients feel better faster. As a prophylactic, an indication approved in 2000, Tamiflu® is labeled for use by adults and adolescents 13 years of age and older, although data on children one year of age and older have recently been submitted to FDA for
review. Tamiflu® has a low likelihood of clinically significant drug interactions and is generally well-
tolerated, with nausea and vomiting being the most frequently reported adverse events. Tamiflu® is
available in both capsule and oral suspension form.

In congressional testimony delivered last month, CDC Director Dr. Julie Gerberding
reaffirmed that Tamiflu® “is the only antiviral at this time shown to be effective against the H5N1
avian influenza virus in Asia.”14 The efficacy of Tamiflu® against avian influenza has been
demonstrated in animal studies by leading researchers, in vitro data, and practical experience during
an avian influenza outbreak in the Netherlands.15 Further, evidence derived from infected humans
and animals suggests significant systemic involvement of the H5N1 avian virus. Importantly, in
contrast to an antiviral drug requiring inhalation, orally ingested Tamiflu® has been shown to be
systemically active in humans. Accordingly, the WHO has recommended use of Tamiflu® in those
potentially exposed to avian flu in Asia.16

Recent news reports have highlighted the resistance to the antiviral drug amantadine due to
veterinary use of the drug in China. To the best of our knowledge, no comparable veterinary use
has occurred with respect to Tamiflu®, and we certainly do not advocate such use. While a
possibility exists for an influenza virus to emerge with decreased sensitivity to any antiviral drug, the
Tamiflu®-resistant viruses isolated in humans to date do not appear to be effectively transmissible.17

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14 The Threat of and Planning for Pandemic Flu: Hearing Before the Subcomm. on Health of the House Comm. on Energy & Commerce
109th Cong. (May 26, 2005) (Statement of Dr. Julie Gerberding).
15 I.A. Lemon et al., The Neuraminidase Inhibitor GS4169 (Oseltamivir Phosphate) is Efficacious Against A/Hong Kong/156/97
(H5N1) and A/Hong Kong/1074/99 (H5N2) Influenza Viruses, Avian Pathol. 31 (2000).
16 World Health Organization, WHO interim Guidelines for Health Monitoring of Persons Involved in Caring for Animals Potentially
17 Data collected from patients treated with Tamiflu®, at its approved dose and for the approved treatment duration, demonstrate an overall incidence of resistant virus of only 0.4 percent in adults and four percent in children aged one to
demnstrate an overall incidence of resistant virus of only 0.4 percent in adults and four percent in children aged one to
twelve. All of the resistant virus strains were found unlikely to spread within a community, even under conditions of
Population sampling also indicates that resistance to Tamiflu® is very infrequent. To ensure Tamiflu® remains effective against the influenza virus, Roche does not recommend strategies which may utilize lower doses or shorter duration of therapy compared with the recommended dose.

For the prevention of influenza in those 13 years or older, Tamiflu® can be administered once a day for at least 7 days following close contact with an infected individual who demonstrates characteristic symptoms of influenza. Tamiflu® can also be taken for up to 6 weeks for seasonal prophylaxis if influenza is circulating in the community. However, the approved dose for the treatment of influenza – 75mg twice daily for five days – is expected to represent the minimum required for the management of an influenza pandemic.

If integrated into a strong pandemic preparedness and response plan, Tamiflu® could be critical both as a stopgap intervention pending the availability of a vaccine, and to treat or prevent further infections once a vaccine is available. During a pandemic, there will be heightened awareness of influenza and – with a functioning infrastructure and appropriate prepositioning – rapid treatment can be achieved.

ALTHOUGH ROCHE IS TAKING STEPS TO INCREASE TAMIFLU® PRODUCTION, THE U.S. GOVERNMENT MUST MAKE CONTRACTUAL STOCKPILE COMMITMENTS TO ENSURE A ROBUST U.S. ANTIVIRAL DRUG SUPPLY

As noted, both HHS and the WHO include stockpiling of antiviral drugs as a central component of their developing plans for influenza pandemic preparedness. The Infectious Diseases Society of America (IDSA) and the WHO have recently acknowledged that Tamiflu®, in particular, is uniquely suited to pandemic stockpiling, for several reasons: (1) its efficacy against influenza types A and B; (2) the absence of a known Tamiflu®-resistant virus transmissible in humans; (3) the product’s five-year shelf life; and (4) its capsule formulation.
It is imperative that Tamiflu® be stockpiled in advance of the outbreak of a pandemic because inherent complexities in production severely limit capacity to rapidly meet large-scale demand arising once a pandemic occurs. The manufacturing process for Tamiflu® is complex, and takes 8-12 months from raw materials to finished product. The process involves many intermediate steps, including a unique starting material, and a potentially explosive production step that can be carried out only in specialized and costly facilities. Given these complexities, significant lead time is needed to increase production capacity and build stockpiles of the quantity required for an influenza pandemic. The historical commercial, seasonal market for Tamiflu® has been modest in relation to pandemic stockpiling needs and would quickly be depleted in the event of a pandemic.

Historically, Roche has produced enough Tamiflu® to meet the seasonal influenza demand. We have worked diligently to educate health care professionals and patients on the appropriate use of Tamiflu®, seeking to expand the seasonal market while not undermining public health messaging regarding vaccinations. This educational process has resulted in steady growth in Tamiflu® prescriptions in the United States in recent years, from roughly 700,000 in the 1999-2000 flu season to over 1.7 million in the most recent flu season. In contrast, the IDSA recommends that the government stockpile enough antiviral drugs to treat up to 50 percent of the U.S. population, or almost 150 million patients.

Roche has been proactive in recognizing and responding to public health needs. For example:

- To achieve levels of production needed for stockpiling, Roche doubled production capacity at our European facility from 2003 to 2004, and we are doing so again during 2005. Roche plans additional expansion of production capacity for Tamiflu® in 2006.
We have also built a U.S.-based supply chain that, when launched later this year, will result in an increase in total global Tamiflu® active pharmaceutical ingredient and capsule production capacity of nearly eight-fold over production capacity in 2003.

Roche developed special U.S. packaging for stockpiled Tamiflu® in order to extend dating and ease distribution and administration.

We discovered and developed a synthetic process for manufacturing the chemical used in the initial production step, which will ultimately greatly reduce reliance on natural sources.

Roche has also been working with the WHO, providing supplies of Tamiflu® for the avian flu outbreaks to date. We are now working with WHO to establish a rapid response stockpile in an attempt to slow or halt the virus at its origin.

Roche has received and will fill — on schedule — pandemic stockpile orders and letters of intent for Tamiflu® from 30 countries worldwide. In fact, countries such as the United Kingdom, France, Finland, Norway, Switzerland and New Zealand are ordering enough Tamiflu® to cover between 20 to 40 percent of their populations. In contrast, HHS stockpile purchases to date total approximately 2.3 million courses of treatment — or enough to treat less than one percent of the U.S. population. We are in discussions with the U.S. government regarding an expanded commitment to procure supplies of Tamiflu® for the national stockpile. Based on such commitments, and as we have done to date, Roche is more than willing to work with HHS to further increase capacity in order to build a robust national stockpile.

Alerted to the pandemic threat, governments now have an unprecedented opportunity to attempt to minimize the catastrophic loss of life, debilitating illness, and enormous economic costs that a pandemic could wreak on the United States and the world. If I can leave you with three messages from my testimony today, they are the following. First, there is a consensus by global health authorities that Tamiflu® is an important tool in pandemic influenza preparedness and
response. Second, other nations are currently well ahead of the United States in Tamiflu® stockpiling, and we urge the U.S. to make commitments now – and sustain these purchases over time – to ensure an adequate stockpile. Finally, I want you to know that the availability of Tamiflu® as part of a robust pandemic response remains my top priority as Chief Executive Officer of Hoffmann-La Roche.

We at Roche want to continue to work closely with this Committee, HHS, and governments around the world to assist in ensuring our pandemic preparedness. On behalf of Roche, thank you for highlighting the importance of this critical public health issue. Dr. Iacuzio and I will be pleased to answer any questions you may have.
Chairman Tom Davis. Well, I thank all of you for your testimony. As I noted, your entire testimony is in the record, and questions will be based on that. Let me start off.

Dr. Milligan, let me start with you. In your opinion, has the United States stockpiled a sufficient amount of Tamiflu to prepare against the threat of a flu pandemic?

Dr. Milligan. If you compare the United States to governments around the world, it is woefully inadequate and way below the levels that would be recommended by not only U.S. health authorities, but by world health authorities. So I believe it is far too low.

Chairman Tom Davis. If something were to occur here, how quickly could we be able to get this out to the population? If the United States were to come in and order millions of more doses tomorrow, how quickly would it be before they could receive it? I will ask either you or Mr. Abercrombie, if there is a consensus there.

Mr. Abercrombie. Well, as I stated, Mr. Chairman, it takes 8 to 12 months to manufacture Tamiflu. It is a very complex multi-step process involving, at one step, potentially explosive material. We have done everything we can to accelerate that process; we have increased production capacity eight-fold. So we cannot rely on the ability to flip a switch and suddenly make large quantities in the event that a pandemic breaks out. That is why it is crucial to stockpile large quantities well in advance of a pandemic.

Chairman Tom Davis. Do you agree with that, Dr. Milligan?

Dr. Milligan. I actually disagree with that, because you can in fact stockpile large amounts of the active pharmaceutical ingredient. So you can stockpile significant amounts, and this stores virtually indefinitely at refrigerated conditions.

Chairman Tom Davis. So the ingredients you can store separately?

Dr. Milligan. The ingredients you can store. The rate-limiting step, then, becomes the capsuling process. And that would require significant orders from governments in order to fill those, because once you make a capsule, it starts to expire.

Chairman Tom Davis. How long does it take to capsulize it, is that pretty quick?

Dr. Milligan. Depends on how many production lines you have and your commitment to that. Making an individual capsule is very fast, but making tens of millions or hundreds of millions would require multiple production lines.

Mr. Abercrombie. If I can just respond to that. In fact, we do store large quantities of the raw materials, predominantly here in the United States, because the United States is the primary site of moving those materials into finished product. And even by storing large materials, it is about a 6-month process before you can, from that point, have finished material on the marketplace.

Chairman Tom Davis. The shelf life is what, at least 5 years?

Mr. Abercrombie. The approved shelf life is currently 5 years. We have worked with the Government to extend the shelf life. The Government is working with the strategic national stockpile to determine if that can be extended in the event of a security problem with a pandemic.
Chairman Tom Davis. You heard our first panel basically say that we need to have more of this. This is the stopgap until you develop your vaccine. OK.

Dr. Crosse, the GAO has previously reported that regional planning between States is inadequate to respond to bioterrorist attacks. The response to an infectious disease such as influenza is very similar to bioterrorism. Did we see effective regional cooperation and information sharing during the flu vaccine shortage last fall?

Dr. Crosse. We saw some. I think that there are some established networks that were already in place. I think that has increased. Last year, however, it was primarily something that was centralized with CDC, so there was much greater centralized control of the distribution once the shortage was identified. I think that we did see some cooperation. Minnesota already heads a multi-State purchasing cooperative for the purchase of influenza vaccine, so that is some regional cooperation that already exists. Dr. Selecky talked a little bit about some regional activities in the Northwest. But it is not something that is true in every part of this country.

Chairman Tom Davis. What States were most successful in dealing with last season’s flu vaccine shortage?

Dr. Crosse. Well, in part it was States that had ordered from Santa Fe, and so they were fortunate in that their supplies were not as limited. But also it was States, I think, who had done more prior planning.

In particular, we saw success in Minnesota, which had an adequate supply and, in fact, had enough vaccine that they were able to offer vaccine to other States. California had a pretty high success rate in reaching populations. Some other States, though, had much more difficulty. Both Maine and Florida, among the States that we visited, had a lot of difficulty in covering their high-risk populations and did not have the same sort of vaccination rates that they had hoped to achieve.

Chairman Tom Davis. Dr. Selecky, during last year’s flu vaccine shortage, some States ended up having adequate supplies of vaccine to meet the demand from high-risk groups, and were even able to offer vaccine to some lower risk. Other States couldn’t even meet the demands of the high-risk groups. Now, Chiron has recently announced that their production rates may be short again this year. Better than last year’s, but be short of what they had hoped.

Does ASTHO have recommendations about how distribution among the States might be more evenly achieved?

Ms. Selecky. Actually, ASTHO would recommend that Centers for Disease Control and the Federal Government bring us into the discussions as quickly as they know that there could be a shortage. Last year I think we were all caught off guard on October 5th, when we learned that we lost one of our manufacturers. And we weren’t quite ready to address the question that was immediate from the public: Where can I get mine today? Will it come to my community?

When we did engage with the Centers for Disease Control, who needed to work with the private manufacturers, I think that is one of the issues that we face in this country; we have a private supply,
a privately delivered product, but a public demand and a public
need. And I think that is what is certainly behind the ASTHO rec-
ommendation that we need a national adult immunization policy in
this country; we need to have incentives, as we mentioned before,
for vaccine manufacturing.

The States are ready to move into that action. Guidance from the
Federal Government is essential. A common message to the public
is very important. But particularly for those of us at States, we had
a sub-rosa network that was about finding out who needed, who
had, how we could get it across lines, as it were, because we don't
control the sales, either, to release from our States. In the North-
west we paid attention to what recommendations by what age that
we would be giving the vaccine, so that we didn't confuse our public
who hears the same media.

There is clearly work to be done, and I would suggest that the
Centers for Disease Control start working with us now about that
potential.

Chairman Tom Davis. Thank you. Thank you very much.

Mr. Burton.

Mr. Burton. Thank you, Mr. Chairman.

Mr. Abercrombie, do they produce Tamiflu in Indianapolis? Is
that your plant that you do production of that?

Mr. Abercrombie. No, sir. The Indianapolis plant is from our
Diagnostics Division. We have Tamiflu production scattered across
other States in the United States, including New Jersey, South
Carolina, North Carolina, California, and Boulder, CO.

Mr. Burton. OK. Your headquarters is there, though.

Mr. Abercrombie. Headquarters for the Diagnostics Division is
in Indianapolis.

Mr. Burton. Is that where you are located?

Mr. Abercrombie. I am located in Nutley, NJ. Pharmaceutical
Division is different from the Diagnostics Division.

Mr. Burton. You need to move to Indiana; it is a great State.

Mr. Abercrombie. I visit there often.

Mr. Burton. I think Mr. Milligan indicated—and I understand you guys have
a little difference of opinion right now—that you could open up
more production lines in order to speed up the production and get
more on the shelf quicker. Because the possibility of a pandemic
does exist, have you considered that, or is your company considering
opening up more production lines to meet the potential demand
for this?

Mr. Abercrombie. Yes, sir. In fact, since 2003 we have increased
the global production capacity eight-fold. We continue to work 24/
7 to do so. At the request of the Department of Health and Human
Services, we have building, have completed a supply chain dedi-
cated right here on U.S. soil that we expect approval from the FDA
in the third quarter.

The real issue, sir, is not capacity from a U.S. perspective; it is
we need firm orders. We are fulfilling orders around the world on
a first come, first serve basis, and the United States is woefully be-
hind the other countries I mentioned in my testimony in providing
orders. But the answer is we will provide whatever capacity is nec-
ecessary to meet global demand for a pandemic. We have and will continue to do so.

Mr. BURTON. Let me make sure I have this straight. You could probably meet the demand that is necessary to protect a large segment of the American population if our health agencies gave you the order to go ahead and produce the product.

Mr. ABERCROMBIE. If we had received a substantial order merely a year ago, sir, we could have delivered tens of millions of courses of therapy this year. Unfortunately, other countries have gotten in line ahead of the United States.

Mr. BURTON. Have our health agencies given you any reason why they have not placed the orders?

Mr. ABERCROMBIE. I can tell you, sir, that me, personally, and other people from Roche have met with senior officials at HHS, CDC, other Members of Congress, and they all agree we need a stockpile, as you heard from the first panel. But I cannot answer why the large order commitment has not yet come.

Mr. BURTON. Mr. Chairman, I would suggest that maybe it would be a good idea for you and the vice chairman and myself and others to sign a letter to our health agencies, HHS, and ask them why they haven’t put in a request or an order for an adequate supply of this. If the risk is as great as it appears to be, and it is uncertain as to when this problem might occur, it seems to me that we ought to be prepared for it. And I would like to join with you, if you see fit, to send a letter of inquiry over there.

Chairman TOM DAVIS. Well, I think we will do that. With a 5-year shelf life, I just think that it makes a lot of sense. And if you heard from the first panel as well, from Federal experts, they seem to agree with that, Mr. Burton. So we will try to do that.

Mr. BURTON. I would be happy to join you in that, Mr. Chairman.

Chairman TOM DAVIS. That would be great.

Dr. Iacucio.

Dr. IACUZIO. Excuse me. I just wanted to add right now we have FDA approved 5-year shelf life. But there is all indication by our chemists that the product is stable longer. And with this shelf life extension program, it could go beyond.

Chairman TOM DAVIS. And it can be used for other strains of flu.

Dr. IACUZIO. Yes.

Chairman TOM DAVIS. Like for last year we could have used this.

Mr. BURTON. Mr. Chairman, I have no more questions. I just think that would be a little stimulus to our health agencies to get on the ball and make sure that we place the order so we will be adequately protected. Thank you, Mr. Chairman.

Chairman TOM DAVIS. Thank you very much.

Mr. SHAYS. Thank you.

Dr. Crosse, it is a bit reassuring that other States have further developed important aspects of public health preparedness. However, it is a concern to know that we still have a lot of work left. And I am not clear as to where the areas of work are.

Dr. CROSSE. I think there are a number of areas of work. One of the ones we highlighted today is in planning to deal with any large-scale infectious disease outbreak, be it pandemic influenza or
any other emerging infectious disease in terms of the hospital capacity and the healthcare work force capacity. This is something that there has been a stream of Federal funding to assist in that effort, but it is still not adequate to deal with a kind of pandemic situation where we believe that hospitals would be overwhelmed.

The other efforts that have benefited from some funding from the Federal Government are in planning for infectious disease outbreaks. There has been some planning at the local level on how to run mass immunization campaigns, but we realized this past winter that there are still many locations that were not set up or not staffed, or had not yet determined how they could run through the public health department a mass immunization effort. That was something that was supposed to have been worked out when they were working on small pox vaccination campaign, but we realized that there are still communities where this is a major challenge.

Mr. SHAYS. Ms. Selecky, has the dissemination of critical information during previous flu seasons to State and local government officials and health institutions been adequate, and how could it be improved?

Ms. SELECKY. The Centers for Disease Control is just completing a round of regional meetings with all of us in the States to learn the lessons from the past and to prepare in better ways for the future. So work continues to be done on that. There is always something new to learn, and whether it is our State plan, it needs to be exercised and then revised.

And to pick up on a point made by Dr. Crosse, in the tri-cities area, where Hanford is, actually, the local health department was the only provider of flu vaccine in the community, in 3 days gave out the 10,000 doses they were lucky to have, on October 7th, 8th, and 9th, using mass vaccination and the plans that we had for any kind of mass vaccination. The State of Arkansas did much the same.

We continue to learn from those, but as I expressed in my testimony, we are quite concerned that we get additional priorities placed on us for use of the cooperative agreement for preparedness, including the pandemic flu planning at, though, an Administrative decision for a reduction. Clearly, the pandemic flu planning is absolutely essential for the protection of our general public.

Mr. SHAYS. I am not quite clear what kind of guidance is being provided by the Federal agencies and to State and local officials to help prepare them to handle a significant outbreak. So let me ask you this. How has the Federal Government supplemented your response efforts in handling the various public health threats that have surfaced in your jurisdiction?

Ms. SELECKY. Clearly, the work that has been done around the strategic national stockpile is work that is new over the last several years of public health preparedness, and particularly with all the emphases since 2001. So the fact that there is stockpiling going on, the number of stockpiles available to the Nation have increased, the practice that we do with our Federal partners on that distribution is additional help.

We are all waiting for the next draft of the Federal pandemic flu plan so that we can revise our State plans as appropriate. But States have not sat back and just waited for that to come out. So
that is one where there is a pull me, push me relationship going on, clearly.

The work that is done with our epidemiologists in our laboratories, being able to do surveillance and identify flu, has definitely increased. However, we continue to be at the mercy of what is in the stockpile, what is purchased, and that is clearly a Federal asset and not a State or local asset.

Mr. Shays. Thank you.

Dr. Hearne, we have heard that some States are experiencing a shortage of trained public health specialists and epidemiologists. How serious is this crisis? First, is it a crisis? And, if so, how serious is it? And what steps can and should be taken to improve training for healthcare workers?

Dr. Hearne. Across the board we have found—whether it is epidemiologists, lab scientists, even some of the critical environmental scientists who would respond in a chemical bioterrorist event—there are huge workforce shortages. It is perhaps one of the greatest problems facing our public health systems from State to State. A report that we put out last year, “Ready or Not,” identified those gaps and identified some of the recommendations to go forward with this.

I think it is an area that must be significantly addressed, particularly as we are talking about beefing up the stockpile, getting supplies. You need to have those front line forces who would do the distribution of those materials, or rapidly identify an outbreak and hopefully contain it before you even need those materials. That is, first and foremost, job No. 1 that we need to focus on with public health.

Mr. Shays. Let me ask you has vaccination as a primary strategy for protecting individuals who are at greatest risk contributed to the lack of antiviral production capacity in the United States?

Dr. Hearne. With antiviral or vaccine? I am sorry.

Mr. Shays. Antiviral.

Dr. Hearne. One of the issues is—as we have been looking at just stockpiling—this is a very new effort that has been ramped up in just recent years since September 11th. We have recognized that we have critical materials missing. Antivirals have not been the top priority, but it is now bouncing up to the top as we are starting to recognize the seriousness and potential severity of a pandemic.

Mr. Shays. So the question, though, as we are looking to protect the folks at the greatest risk, has that impacted our supply?

And I will allow others to respond.

In other words, we don’t stockpile it, we are out there using it in anticipation because they are at risk, correct?

Dr. Hearne. Well, one of the lessons we learned from the previous shortage in the flu vaccine is that we didn’t have those distribution systems in place. We had challenges of identifying who was even most at high-risk, how to get them out there, and how to assure that. This is, again, a balancing act of making sure that we are creating sufficient demand for materials so that we can have either ready-to-use materials and also stockpiles, and the distribution mechanisms to effectively reach those most at need.

Mr. Shays. The staff would like this question asked of Roche. The CDC conducts a strong flu vaccine campaign in the early fall
of every year. Does Roche actively market Tamiflu during this time? How does Roche’s marketing strategy compliment CDC’s strong immunization method? And do you believe that heavier marketing by Roche during the annual flu season could have increased demand and production capabilities for Tamiflu over the years?

Mr. Abercrombie. Since launching Tamiflu, we have acted responsibly to ensure that we convey to physicians the role of both vaccines and Tamiflu. We encourage that all patients who need to be vaccinated be vaccinated. There is clearly a role for vaccines. And then there is a role for Tamiflu, in case you are infected with influenza. We usually, including last season, actually disseminate the CDC guidelines so that we are very transparent and up-front with that. We do not want to indiscriminately advocate Tamiflu use, we want to make sure it is used consistent with the guidelines. And there is a role for both in normal influenza, as well as a pandemic.

Mr. Shays. Let me ask is there any question that you all want to put on the record? In other words, do you want to ask yourself a question that you can then answer to put on the record? Is there anything that the record would be incomplete without that answer being asked? It is a serious question to ask, it is usually my best question.

Yes, Ms. Selecky.

Ms. Selecky. I would have you ask me the question as to what intervention States are prepared to take should we be faced with pandemic flu.

Mr. Shays. That is a great question. Why don’t you answer it?

Ms. Selecky. And, if so, I think what we have to do is absolutely look at it as a comprehensive approach. Yes, antivirals are important. Yes, vaccine and routine every-year vaccine is essential. But we must be able to do the enhanced disease surveillance. I recently was at a global health summit in the Pacific Northwest with 16 countries from the Pacific Rim who were represented, including those countries that have avian influenza in human populations. The head of the World Health Organization and all of the leading medical and governmental folks from those countries said you must have public health infrastructure in place if we are going to even think about addressing a pandemic of the proportion we are all concerned about.

So it is about surveillance, it is about your State and local public health system. It is also about community containment strategies, making sure we use things like quarantine and isolation appropriately, or simple things like cover your mouth or stay home, those basic public health things.

A third would be antivirals; a fourth would be vaccine; and clearly the issue of healthcare system surge planning. We must be at the table with our hospital partners. We must understand that we may stop certain activities if we were ever hit with a pandemic. But we have all got to deal with—every one of us, State, Federal, local—good and important risk communication. The public expects to tell them what they know in a way that they can figure out how to protect themselves and their families.

Thank you.
Mr. SHAYS. Thank you. Thank you for that question and thank you for that answer.

Is there any other question that you need to ask yourselves here? Anyone else want to put anything else in the record?

[No response.]

Mr. SHAYS. Well, let me just thank you. Let me just ask this last question. What country does this the best, protects the public the best? Who would be the best model around the world? And if you choose a country, tell me why. Ms. Selecky?

Ms. SELECKY. Well, I will venture a guess. And it is only because of our recent experience with British Columbia. Because we are both a State and a province that have such international trade from the east. And what we look at is the systems are so different. When I sit with my colleagues from Canada and understand that the healthcare system is the governmental system, and that a singular decision is then carried out in a way that is very different with the suasion that we have to do with our private partners, the private suppliers, etc.

It is a very different system. So I am not sure it is better, but, indeed, when they were facing.

Mr. SHAYS. When it comes to dealing with an epidemic, a pandemic, they may be better able to deal with it, given that they have a more public process throughout?

Ms. SELECKY. They are easier to get a common decision through a number of partners, where I, as a State health official, need to work with my public and private hospital systems and convince them. They do it with us.

Mr. SHAYS. It just triggers a reaction from me. We are not going to see that system in the United States, so it is incumbent on all of us to find a way that we make the private and public sector work better. And giving better direction to the private sector, providing financial incentives, dealing with some risk that you encounter, all of that, it seems to me, will play a role in our providing a better service.

So let me end with that, if I could, and thank you all for this hearing. Thank you for being here. Thank you for helping your country do a better job.

With that, we will adjourn this hearing.

[Whereupon, at 12:38 p.m., the committee was adjourned.]

[NOTE.—The Association of State and Territorial Health Officials November 2002 report entitled, “Preparedness Planning for State Health Officials, Nature’s Terrorist Attack Pandemic Influenza,” may be found in committee files.]

[The prepared statements of Hon. Dan Burton, Hon. Jon C. Porter, and Hon. Diane E. Watson, and additional information submitted for the hearing record follows:]
Mr. Chairman, thank you for convening this important and timely hearing to recognize the ever-growing danger of a flu virus striking the United States, and whether or not the United States is adequately prepared to handle a global communicable disease outbreak. I look forward to hearing testimony from our witnesses and hope that by day’s end we will have a better idea of how to address this potentially deadly outbreak.

As you know, U.S. health officials have warned us for years that the largest public health threat facing the world today is a flu pandemic. In fact, many officials have estimated that an influenza outbreak could lead to the deaths of more than a half-million people. The United States must continue to do more in order to ensure that we will not be adversely affected by an influenza pandemic. Unfortunately, the United States has experienced – over the recent year – major vaccine shortages. With seasonal influenza deaths of 36,000 and 114,000 hospitalizations, we must work together to address this growing concern.

As we all know, early detection and rapid development of effective vaccines is the best way to defend the public against the influenza virus. One such company who is actively helping to defend the public against a potential pandemic is Roche, Incorporated. As the Member of Congress who has the distinct honor of representing the headquarters of Roche Diagnostics – and its 3,500 employees – in Indianapolis, Indiana, I have had the opportunity to become familiar with the tremendous contributions that Roche and its employees have made to healthcare and diagnosticians, and I am impressed with how Roche’s investments in research and innovation have yielded inventions to help thousands of people throughout the world. As a result of these investments, people suffering from numerous diseases can now successfully manage their conditions, and doctors and hospitals can more accurately identify illnesses and effectively treat their patients according to the patients’ individual needs.

One such investment in innovation is Tamiflu – the first oral medication effective against types A and B of the influenza virus. As I have been informed, Tamiflu is the number one antiviral in the U.S. for treatment and prevention of influenza. Roche has invested significant resources in the development and approval of Tamiflu to bring this product to market as quickly as possible. In fact, Roche has increased manufacturing capacity eightfold in recent years to meet commercial and government pandemic stockpile goals. Moreover, I would like to personally welcome Mr. George Abercrombie – Chief Executive Officer and President – from Hoffmann-La Roche, Inc.

Once again Mr. Chairman, thank you for highlighting the importance of this critical issue. I look forward to hearing the testimony of the Committee’s witnesses.
CONGRESSMAN JON C. PORTER (R-NV-3)
COMMITTEE ON GOVERNMENT REFORM
“The Next Flu Pandemic: Evaluating U.S. Readiness”
June 29, 2005

Mr. Chairman, thank you for holding this hearing today. I would also like to thank the witnesses for being here today.

As stated in the Government Reform Committee’s background memorandum for this hearing, history indicates that flu pandemics can be expected to occur three to four times each century. Pandemics can be devastating, as seen in the Spanish flu pandemic where 40-50 million died circa 1918, and the next pandemic could occur within the next five years. The scary fact is that, with the advent of aircraft and the vast improvement of various modes of transportation, the next flu pandemic has the potential of being even more devastating if we are not properly prepared.

With the increase in technology we have seen in recent years has come an increase in medical innovation. Flu shots have been able to keep many millions of people from falling ill; however, vaccines alone cannot stop the flu from spreading. Furthermore, last year, Americans witnessed a vaccine shortage where thousands of individuals were unable to get a flu shot. As the flu vaccine shortage showed, our government needs to be prepared on multiple levels with respect to having enough vaccines or anti-virals to sustain the American people should a flu, or other type of pandemic, occur.

Mr. Chairman, I am glad that we are holding this hearing before this year’s flu season starts. I believe that last year’s vaccine shortage was truly an exercise in our nation’s ability to effectively produce and distribute flu vaccines. We should learn from these mistakes and ensure that our country is not left in a vulnerable position when the next flu pandemic hits.

Again, thank you for holding this hearing today, and I look forward to hearing the testimony from the witnesses.

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Opening Statement
Congresswoman Diane E. Watson
Government Reform Committee
6/30/05

Thank you Mr. Chairman. The Government Reform Committee has an important public service to perform in regards to the ever-present flu virus. Biological preparedness is considered crucial in the current world climate. Our government has limited control over a natural phenomenon that will threaten citizens every year. Flu pandemic has the ability to cause death in catastrophic proportions.

In its cyclical nature, the annual flu epidemic is a situation that our federal, state, and local health officials try to plan for. Flu pandemic is a worldwide event that is also cyclical. This government would be remiss to not be properly prepared and informed about options to protect the public.

With only two FDA approved vaccine manufacturers (Chiron and Aventis) producing flu
vaccines each year, Congress must consider what can be done to strengthen the market and increase domestic production capabilities. Is a stockpile of antiviral drugs the best way to approach the absent vaccine?

Mr. Chairman, I am concerned about our national position in a very sensitive health care area. In the future, should a flu pandemic occur, it can be theorized that the UK could restrict Chiron's vaccine supply, again resulting in the loss of half of the U.S. flu vaccine supply. Currently, Aventis has the only U.S. based flu vaccine production facility in operation. To address the flu vaccine issue Congress must work to reinvigorate the domestic manufacture of vaccines.

Mr. Chairman, I look forward to today's testimony and the positive solutions that our witness can provide. I am interested to hear their assessment of the usefulness of antiviral drugs. I am encouraged by the antiviral ability to stem the conditions of the flu. Congress must weigh the feasibility of supplying the suggested antiviral dosage for 25% of the population or decide if the resources should be balanced or directed to another proactive path. We need a much
better system in place to accommodate flu vaccine shortage or increased demand situations. I urge Congress to move forward in the decision making process. I again commend our Committee for a quick response to a serious public concern.

I yield back the balance of my time.
PHILIP HOSBACH
VICE PRESIDENT, IMMUNIZATION POLICY AND GOVERNMENT AFFAIRS
SANOFI PASTEUR

BEFORE THE UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM

REGARDING
THE NEXT FLU PANDEMIC: EVALUATING U.S. READINESS

WRITTEN TESTIMONY

6/30/05
Sanofi pasteur is committed to working with the federal government to develop a safe and effective vaccine to protect the American public in the event of an influenza pandemic. Our common goal is to provide sufficient vaccine for 300 million Americans within the first 12- to 18-month period of a pandemic, and we welcome the chance to provide the committee with our perspective on this important public health issue.

Sanofi pasteur, the world’s largest influenza vaccine manufacturer, also produces vaccines against more than 20 different diseases. Worldwide, we produce almost 1 billion doses of vaccines annually. The company, which employs more than 9,000 employees worldwide, is headquartered in Lyon, France. Sanofi pasteur’s US operations are located in the Pocono Mountains in Swiftwater, Pa., at a site where vaccine has been produced for more than 100 years. Influenza vaccine has been produced in this facility for more than 30 years and 95% of this vaccine is used exclusively to supply the United States. Sanofi pasteur also has an influenza vaccine production facility in France that supplies other markets.

During the past decade, sanofi pasteur has reliably and consistently increased production of influenza vaccine in the US. Last year, we produced 58 million doses for the US market. We continue to expand our vaccine manufacturing capacity in Pennsylvania and have embarked on the largest infrastructure investment in the company’s history, spending almost $80 million to build a new formulation and filling facility. We are also in the final design phases of our influenza vaccine facility expansion, which will significantly increase our US production capabilities.

Pandemic Overview

An influenza pandemic is a global epidemic that has the potential for severe morbidity and mortality.
Three influenza pandemics occurred during the 20th century: the 1918-1919 Spanish flu pandemic, the 1957 Asian flu pandemic and the 1968 Hong Kong flu pandemic. The Spanish flu pandemic was the most severe, causing over 500,000 deaths in the US and an estimated 20 to 40 million deaths worldwide.

The prospect of a pandemic is taking on increasing urgency because of the emergence of an H5N1 avian influenza strain in Southeast Asia 17 months ago. It continues to circulate and has the potential to mutate and become a human pandemic strain. As of June 16th, it has infected at least 103 people and killed more than half of its victims. This is a completely new strain and epidemiologists believe the American population would be at risk if it spreads between humans.

Many experts believe that if this H5N1 virus sparks the next pandemic, it would most closely resemble the 1918 pandemic in terms of morbidity and mortality. According to the World Health Organization (WHO), the next pandemic is likely to result in 1 to 2.3 million hospitalizations and 280,000 to 650,000 deaths in industrialized nations alone. The US Centers for Disease Control and Prevention (CDC) estimated that as many as 207,000 Americans could die and up to 734,000 could be hospitalized during the next pandemic. Other estimates are even higher. For example, extrapolating from the 1918-1919 Spanish Flu, the US alone could face more than 1 million fatalities.

Studies have estimated certain costs of an influenza pandemic in the US as high as $200 billion (FY2005 dollars). These estimates include only direct costs of medical care and indirect costs of lost productivity and

1 Cumulative Number of Confirmed Human Cases of Avian Influenza A(H5N1) Reported to WHO. See WHO site listing under Communicable Disease Surveillance and Response (CSR).


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sanofi pasteur
The world leader in influenza research, development and manufacturing.
mortality rates. Some experts have predicted that a major pandemic could bring the global economy to a halt.¹

Sanofi Pasteur recognizes the urgency of adequate preparation for a pandemic event and is taking steps to be ready:

**Progress to Date**

We believe the expertise of vaccine manufacturers, particularly those with a track record in influenza vaccine production and distribution, should be utilized early in the planning process. Vaccines, by their very nature, are challenging to develop, produce and distribute. Manufacturers have a unique understanding of these challenges and can provide valuable process and policy input. Our knowledge and experience with the complexities of vaccine supply make industry an essential partner in pandemic planning and policy formulation.

The enormous public health threat posed by a potential pandemic prompted Sanofi Pasteur to establish an internal working group to examine pandemic planning. We formed a global working group to examine preparedness, production, communications and distribution issues. In the US, we have worked in cooperation with the US Department of Health and Human Services (HHS) to exchange ideas on how best to prepare for and respond to a pandemic influenza outbreak, and have provided significant input into the initial draft of its pandemic plan.

We have moved forward with clinical research and vaccine production because of important funding provided by Congress and the Administration. In May 2004, sanofi pasteur entered into the first of four pandemic agreements with the US government. The National Institute of Allergy and Infectious Diseases (NIAID) contracted with us to produce an investigational influenza vaccine based on the currently circulating H5N1 avian influenza virus strain. On March 10, 2005, in accordance with that agreement, sanofi pasteur delivered more than 8,000 investigational doses, which currently are being used in NIH-conducted clinical trials.

In September 2004, the company was awarded a second contract by HHS to produce two million bulk doses of an attenuated version of the same H5N1 avian influenza virus strain of vaccine. This contract represents an important step in gaining experience producing pandemic influenza vaccine on a large scale. This is critical because scale-up presents unique challenges in vaccine production. Part of our agreement is to determine the stability of this vaccine, which is important for understanding our ability to establish an H5N1 reserve.

Sanofi pasteur subsequently entered into a third agreement with HHS to establish and maintain flocks of egg-laying hens and to maintain other essential supplies. The goal is to ensure our ability to manufacture pandemic influenza vaccine at current full capacity levels on a year-round basis. Until now, egg availability has existed only on a seasonal basis to support normal influenza vaccine production. The agreement also calls for sanofi pasteur to manufacture, on an annual basis, investigational influenza vaccine of a candidate pandemic-like strain. Each year, HHS will identify the strain to be used in the investigational lot and will provide the reference virus on which each investigational lot will be based. This will enable us to gain experience working with various viral strains that might be similar to the next pandemic strain.
Finally, in April 2005, sanofi pasteur was awarded a fourth contract from HHS. This was to speed the development process for a new cell culture influenza vaccine in the US and to deliver plans to establish a US-based cell culture influenza vaccine manufacturing facility.

**Required Action:**

We are encouraged by the increased attention pandemic planning is receiving from the US government, industry, international agencies and key stakeholders. However, unresolved critical issues remain. The failure to address these challenges could adversely affect our country’s ability to respond to a pandemic event.

I would like to briefly outline steps that should be taken to help the country better prepare for a pandemic and minimize the effects should one occur.

A first step is to **steadily increase interpandemic influenza immunization rates**. Manufacturers will respond to increased and predictable demand by producing additional vaccine to fulfill this demand.

This is important because our ability to produce and administer large quantities of influenza vaccine during interpandemic periods will enable a more rapid response during a pandemic. Increasing capacity in dedicated influenza vaccine production facilities and establishing an infrastructure that can deliver vaccine and immunize large numbers of people in a short period of time is a key component of pandemic preparedness.

To that end, Congress, industry and stakeholders need to work together to encourage higher influenza immunization rates in accordance with HHS’ Healthy People 2010 immunization goals. The objective is to
immunize approximately 180 million Americans. However, as a nation, we have never immunized more than 85 million people in any given year. This is unacceptable. A steady and sustained increase in interepidemic demand would give current manufacturers the confidence to continue expansion plans and new companies the incentive to enter the market.

Second, we need to ensure a proper combination of private and public sector distribution of vaccine in the event of a pandemic. We believe that while it will be important to establish mechanisms for mass immunizations and clinics, the private physicians’ offices will continue to play a vital role as well. During a typical influenza season, the private sector distributes more than 85% of the nation’s influenza vaccine supply. The private market provides maximum flexibility in vaccine distribution and allows us to reach large segments of the US population in their “medical homes.” This includes the elderly, who should not stand in long lines and may be more comfortable with their personal physicians.

Last year’s influenza vaccine shortage illustrated sanofi pasteur’s unique expertise in processing and shipping product to virtually any location in the United States within 24-48 hours. We shipped vaccines to end-users in accordance with the CDC’s recommendations and distribution plan. Further, the unprecedented degree of collaboration between sanofi pasteur and the CDC underscores our willingness to work with public agencies to protect America’s public health. This year, sanofi pasteur has modified our ordering process to provide that, in the event of another shortage, available vaccine reaches high-risk people first. All of our “pre-book” customers are being asked to estimate what percentage of the vaccine they are requesting will be used for priority patients. The systems utilized to collect these data and the ability to easily identify priority recipients, as specified by federal, state and local governments, will be key in protecting the public health in the event of a pandemic. We also believe that there should be greater funding for coordinating
communications between federal and state agencies and the private sector regarding vaccine allocation issues.

Pandemic influenza vaccine liability protection is another critical issue in pandemic preparedness. A special compensation and liability protection program will need to be established similar to the 1976 swine flu and 2002 smallpox model. Liability protection for companies is essential to ensure that manufacturers are able to fully participate in the development and licensure of a pandemic vaccine. This is of paramount importance. The new program should be completely distinct and separate from the existing Vaccine Injury Compensation Program (VICP). It should focus exclusively on liability protection for a monovalent influenza pandemic vaccine, precisely the type of vaccine that will be produced in a pandemic event. The failure to offer liability protection on a timely basis could have profound implications for the actual testing and development of large-scale production of vaccine, leaving the nation unprepared. It is important to address liability issues before a health emergency arises. This ensures that pandemic vaccines will be developed, economic costs will be mitigated, and the potential for needless and costly litigation will be curtailed.

We strongly urge Congress to consider -- and establish -- liability protections that are as strong as those afforded providers of smallpox vaccine under the Homeland Security Act of 2002. Vaccine liability provisions ensure that we can bring a pandemic influenza vaccine to market as quickly as possible.

SanofiPasteur is committed to protecting America’s public health in the fight against influenza through vaccinations. We want to commend Congress and the Administration for dedicating time and resources to this critical area. Thank you for giving us the opportunity to express our views on this important issue.