AUTHENTICATED
U.S. GOVERNMENT
INFORMATION
GPO

S. HRG. 108–780

LIABILITY, LICENSING AND THE FLU VACCINE MARKET: MAKING DECISIONS TODAY TO PREVENT A CRISIS TOMORROW

HEARING

BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

WASHINGTON, DC

NOVEMBER 16, 2004

Serial No. 108–46

Printed for the use of the Special Committee on Aging

U.S. GOVERNMENT PRINTING OFFICE

98–460 PDF WASHINGTON : 2005

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2250 Mail: Stop SSOP, Washington, DC 20402–0001

SPECIAL COMMITTEE ON AGING

LARRY CRAIG, Idaho, *Chairman*

RICHARD SHELBY, Alabama
SUSAN COLLINS, Maine
MIKE ENZI, Wyoming
GORDON SMITH, Oregon
JAMES M. TALENT, Missouri
PETER G. FITZGERALD, Illinois
ORRIN G. HATCH, Utah
ELIZABETH DOLE, North Carolina
TED STEVENS, Alaska
RICK SANTORUM, Pennsylvania

JOHN B. BREAUX, Louisiana, *Ranking Member*
HARRY REID, Nevada
HERB KOHL, Wisconsin
JAMES M. JEFFORDS, Vermont
RUSSELL D. FEINGOLD, Wisconsin
RON WYDEN, Oregon
BLANCHE L. LINCOLN, Arkansas
EVAN BAYH, Indiana
THOMAS R. CARPER, Delaware
DEBBIE STABENOW, Michigan

LUPE WISSEL, *Staff Director*
MICHELLE EASTON, *Ranking Member Staff Director*

CONTENTS

	Page
Opening Statement of Senator Larry E. Craig	1
Statement of Senator Herb Kohl	3

PANEL I

Lester M. Crawford, D.V.M., acting commissioners, Food and Drug Administration, U.S. Department of Health and Human Services	4
Mitchell L. Cohen, M.D., director, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, Atlanta, GA	22

PANEL II

Peter R. Paradiso, vice president for New Business and Scientific Affairs, Wyeth Pharmaceuticals, Collegeville, PA	54
Frank A. Sloan, Center for Health Policy, Law and Management, Terry Sanford Institute of Public Policy, Duke University, Durham, NC	68

APPENDIX

Prepared Statement of Senator Susan Collins	91
CDC Responses to Questions from Senator Wyden	91
Statement of the American College of Physicians	93
Statement submitted by the World Health Organization	98
Statement of Paul Strauss, United States Senator, District of Columbia (shadow)	106

LIABILITY, LICENSING AND THE FLU VACCINE MARKET: MAKING DECISIONS TODAY TO PREVENT A CRISIS TOMORROW

TUESDAY, NOVEMBER 16, 2004

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The committee convened, pursuant to notice, at 2:34 p.m., in room SD–628, Dirksen Senate Office Building, Hon. Larry Craig (chairman of the committee) presiding.

Present: Senators Craig, Kohl, Wyden, and Carper.

OPENING STATEMENT OF SENATOR LARRY E. CRAIG, CHAIRMAN

The CHAIRMAN. Good afternoon and welcome, everyone, to this hearing of the Special Committee on Aging.

On September 28, this committee held a hearing entitled, "Combating the Flu: Keeping Seniors Alive." The hearing stressed the seriousness of the disease and the importance of flu vaccines. With 36,000 deaths last year, we cannot underestimate the danger that influenza poses to seniors and to at-risk populations. At that hearing, we were told we could expect to have more flu vaccine this year than ever before.

Unfortunately, those expectations changed dramatically a week later when Chiron announced they would be unable to provide the 48 million doses of vaccine they had anticipated. This announcement dealt a strong blow to the United States preparedness for this year's season. Chiron's alarming situation is, I hope, more than a wake-up call that better long-term flu preparedness is imperative.

As we heard at the September hearing, this is especially true in light of the fact that scientists around the world now estimate or believe that we are especially close to a strong endemic strain of flu that could strike not just this country but the world.

Since October, we have seen outstanding efforts on the part of public health officials, manufacturers, private providers, retailers, and all of those who have worked so hard to minimize the effects of this year's shortage. I would like to congratulate the countless individuals who took immediate action to be sure that the most vulnerable in our country get the vaccine they need. Today, we will hear about that in an update from the CDC and from the FDA on continuing this effort to that end.

Just as important as the swift reaction to this year's shortage is the challenge to make swift decisions to avoid the same problem

next year and the year after. We have absolutely no time to waste in addressing this issue and making the necessary changes to ensure an adequate supply of vaccine in the future. But many questions have yet to be answered, and that is why I decided to hold a hearing now in November during a lame duck session of Congress.

Flu manufacturers are now making decisions in order to fill orders for the next year. We can't wait until Congress is in full swing in February to address next year's supply challenges. By then, it will be nearly too late, especially if Chiron Corporation is unable to start production next year. Flu is a worldwide killer and the need for vaccine is clear, and yet the market has dwindled to the point that the pull-out of just one company has devastated the U.S.'s supply.

The reasons for this dilemma are many. Today's hearing is not about pointing fingers and laying blame. This is about looking at the current situation and gathering the information necessary to make needed policy decisions that will address the flu vaccine problem in 2005 and beyond. In conversations with vaccine manufacturers, health officials, and other stakeholders, three main areas of concern come up time and time again: Liability, licensure, and the stability of the vaccine market. This afternoon, we will hear from four experts that will speak to each one of these issues, I hope.

Senator Evan Bayh, who may be joining us later, and I introduced legislation earlier this year to further address some of the long-term issues. For example, our legislation, S. 2038, would encourage an increase in vaccine production capacity by offering a tax credit for companies to invest in the construction of or the renovation of production facilities. I would like to think we could get that through this year. That is probably very unrealistic. But certainly very early passage of it in this next session of Congress is something that many of us will seek.

So I want to thank you for taking time to participate in the hearing today. Before closing, I would like to comment that I found it very disturbing that my staff and I had a difficult time finding appropriate witnesses to speak to these subjects. The combination of liability concerns and reluctance to openly question the regulatory review and approval process has acted to deter participation in this and other hearings on the topic. Certainly in an open public policymaking process, all should be willing to come forward to be open and frank in what I believe is a critical health care discussion for our nation. Yet, frankly speaking, many were very hesitant.

I want to thank all of you who are here. I have great hope that today's discussion will be a help to lawmakers as we move forward to address this issue. I should note also that the interest in this topic is not limited to just those of us as U.S. citizens. The World Health Organization held an unprecedented summit meeting last week on flu vaccine manufacturers and nations and encouraged them to ramp up plans for dealing with the growing threat of a flu pandemic. They will be submitting written testimony about the summit for this committee.

We have two panels this afternoon. On our first panel, we will hear from Dr. Lester Crawford, acting commissioner of the Food and Drug Administration. We will also hear from Dr. Mitchell

Cohen, director of CDC's Coordinating Center for Infectious Diseases.

On our second panel, we will hear from Peter Paradiso, vice president for New Business and Scientific Affairs for Wyeth Pharmaceuticals, and Dr. Frank Sloan from the Center for Health Policy, Law, and Management at Duke University. Dr. Sloan also chairs the Institute of Medicine's Committee on the Evaluation of Vaccine Purchase Finance in the United States.

Dr. Leyton Reid of Alloy Ventures was scheduled to join us today but unfortunately could not make the trip from California here because of family commitments.

So we thank all of you for being with us, and before I turn to our panelists, let me turn to Senator Kohl, a valuable member of this committee. Senator, welcome.

OPENING STATEMENT OF SENATOR KOHL

Senator KOHL. Thank you, Senator Craig, for holding this important hearing today. The flu vaccine shortage our country is facing has been a wake-up call for all of us. Throughout Wisconsin and across the nation, flu shot clinics have been canceled. Health care providers have scrambled to find supplies of vaccine to serve the most high-risk individuals. Families and senior citizens have worried about their health and the health of their loved ones.

Wisconsin has done its best to deal with the problem. State and local health officials have worked hard to assess the vaccine supply and distribute vaccine to the most needy areas. Healthier people have, for the most part, foregone their flu shots so our more vulnerable citizens could get the protection that they need. But we still face many challenges, we know, as the flu season has only just begun, and so these efforts will need to continue.

While we deal with the immediate shortage, we know we need to make sure that we don't treat this as a one-time freak accident. The shortage has exposed systemic problems, some of which have been known for years. They must be addressed. If we don't act quickly, then we put ourselves at risk of the same situation and even worse happening again.

So I am pleased to join Chairman Craig and Senator Bayh in sponsoring the Flu Protection Act. This legislation takes an important step toward shoring up the flu vaccine market and its distribution system. It has incentives that will help encourage more companies to invest in the flu vaccine market. It will encourage States and the CDC to develop plans for dealing with distribution, whether in a time of shortage or in a potential pandemic. It will educate all Americans about the need to be vaccinated, keeping people healthy and fostering a stable vaccine market.

In a few months, development must begin for next year's flu vaccine. So that means that we must act quickly to address the holes in the current system. I hope and I expect that this hearing will shed more light on the steps we need to take and that Congress will move quickly to take those steps.

Thank you, Mr. Chairman.

The CHAIRMAN. Herb, thank you very much.

Now let us turn to our first panelist and our first speaker is Dr. Lester Crawford, as I mentioned, acting commissioner for the Food and Drug Administration. Doctor, welcome back to the committee.

STATEMENT OF LESTER M. CRAWFORD, D.V.M., ACTING COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. CRAWFORD. Thank you very much. Mr. Chairman, I am Les Crawford, acting commissioner of the Food and Drug Administration. As you know, we are responsible for the regulation and oversight of vaccines. I want to assure the committee and the public who are listening today that FDA takes their concerns about vaccine safety and availability very seriously.

FDA has many important responsibilities related to vaccine safety. Before a vaccine is licensed, the FDA monitors the safety of investigational vaccines. Later, when a manufacturer submits a vaccine license application, we conduct more extensive reviews. If we determine that a vaccine is safe, effective, and that quality and consistency of manufacture have been demonstrated, we will license the vaccine. We also inspect the manufacturing facilities every 2 years.

Influenza vaccine is unique in that its active ingredients change almost every year. This presents special manufacturing challenges. We work closely with manufacturers to facilitate the production of influenza vaccine. We begin working with manufacturers at the earliest stages of vaccine development. FDA and manufacturers conduct tests to assure the safety and efficacy of the vaccine because of the complexity of the manufacturing process. FDA's Center for Biologics Evaluation and Research performs lot release testing on bulk vaccine lots. As a further safeguard, we also evaluate information on vaccine testing performed by the manufacturer.

There has been a very significant increase in flu vaccine production over the past 10 years. However, with the increasing volume of doses needed each year and the decline in the number of influenza vaccine manufacturers, we have a very fragile infrastructure in the influenza vaccine market. For the 2004–2005 flu season, only three manufacturers began production of influenza virus vaccine for the United States market. Chiron Corporation and Aventis Pasteur produce inactivated influenza vaccine. MedImmune, Incorporated manufactures FluMist, a live attenuated influenza vaccine administered intranasally.

On the morning of October 5, 2004, the British Medicines and Health Care Products Regulatory Agency announced a 3-month suspension of Chiron's license to manufacture influenza vaccine. FDA immediately dispatched a senior team of scientists to the United Kingdom to meet with company officials and the regulatory agency for England and also to inspect Chiron's Liverpool manufacturing facility.

On October 15, 2004, after completing its inspection, the FDA determined that it could not adequately assure that Chiron's vaccine met our safety standards. As a result, Chiron will not supply any influenza vaccine to the U.S. market for this season.

In coordination with others at the Department of Health and Human Services, we have been actively exploring all viable options

to secure additional doses of flu vaccine to provide more Americans protection against the flu. Through these efforts, we have been able to increase the available supply of licensed flu vaccines for the U.S. population to 61 million doses for this flu vaccine.

Coupled with that initiative, we have been contacting manufacturers around the world in an effort to identify increased supplies of antiviral medications that will provide further protection and treatment for Americans during this flu season. Next year, Aventis Pasteur Corporation believes they have the capability of producing the same or more doses of influenza vaccine. In addition, MedImmune has indicated that it has the capability to produce ten million doses of FluMist for the 2005–2006 flu season, and as much as 40 million doses by the year 2007.

We will continue to help Chiron address as quickly as possible the manufacturing problems they experienced during this year's production process and are working closely with MHRA in Great Britain in this regard. In addition, FDA has also been encouraging foreign licensed manufacturers to apply for U.S. licensure and we are working to help them achieve this goal.

Looking further ahead, we must develop more efficient ways to produce flu vaccine so we have flexibility to deal with shortages or unexpected problems. In each of the last two budgets, the Department has requested $100 million to shift vaccine development to new cell culture technologies as well as to provide for year-round availability of eggs for egg-based vaccine. We urge Congress to fully fund the $100 million requested for the fiscal year 2005 budget.

To help manufacturers overcome challenges such as the vaccine development problems Chiron is experiencing, FDA has been investing its energy and resources in the important initiatives such as the Current Good Manufacturing Practices for the 21st Century, known as the CGMP initiative. Under this initiative, FDA is working with industry to encourage the use of advanced technologies as well as quality systems and risk-based manufacturing processes to avoid the problems such as those that Chiron experienced.

Once again, thank you for the opportunity. I look forward to the rest of the hearing.

The CHAIRMAN. Doctor, thank you very much.

[The prepared statement of Dr. Crawford follows:]

Testimony
Before the Special Committee on Aging
United States Senate

FDA's Ongoing Efforts to Ensure the Safety, Effectiveness, and Availability of Influenza and Other Vaccines

Statement of
Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 2:30PM
Tuesday, October 16, 2004

Introduction

Mr. Chairman and members of the Committee, I am Dr. Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of the Food and Drug Administration (FDA or the Agency). As you know, the FDA is responsible for the regulation and oversight of vaccines in the United States. I want to assure the Committee, and the public who are here today, that FDA takes their concerns about vaccine safety and availability very seriously. I welcome this opportunity to describe FDA's ongoing efforts to ensure the safety, effectiveness, and availability of influenza and other vaccines licensed in the U.S.

Vaccine Safety

Vaccines have contributed greatly to the health and well being of the people of our nation; however, we must nonetheless be vigilant of any potential safety concern related to vaccines. I will briefly describe some of FDA's vaccine safety activities. In the pre-licensure phase, FDA monitors the safety of investigational vaccines as they are studied in clinical trials conducted under investigational new drug applications. When a manufacturer submits a license application to FDA, we review extensive information describing the manufacture and characterization of the vaccine, the safety and efficacy data from the clinical trials, and we typically inspect the manufacturing facility where the vaccine will be made. In addition, we usually seek advice from our Vaccines and Related Biological Products Advisory Committee on the safety and effectiveness of vaccine candidates. If we determine that a vaccine is safe, effective, and that quality and

consistency of manufacture have been demonstrated, we will license the vaccine.

Post-licensure, we typically review the manufacturer's test results before the manufacturer can release new lots of vaccine to the market. We also inspect the manufacturing facilities every two years. In addition, FDA's Center for Biologics Evaluation and Research (CBER) and the Centers for Disease Control and Prevention (CDC) jointly manage the Vaccine Adverse Event Reporting System (VAERS), a cooperative program for vaccine safety. VAERS is a post-marketing safety surveillance program, collecting information about adverse events (side effects) that occur after the administration of U.S. licensed vaccines. Reports to the VAERS program are welcome from all concerned individuals: patients, parents, health care providers, pharmacists, and vaccine manufacturers. We review these reports on an ongoing basis and obtain additional information as needed.

Influenza Vaccines

To increase our control of this very important disease, efforts are ongoing to increase the availability of influenza vaccine and increase coverage, especially of those individuals at increased risk of complications from influenza. Influenza vaccine is unique among vaccines in that its active ingredients change almost every year and thus presents new manufacturing challenges on an annual basis. Influenza viruses are continuously evolving or mutating, and the

recommendations of which viruses to include in the vaccine each year are based on the surveillance data provided from laboratories worldwide. Early each year, public health experts evaluate the data to determine the strains of virus to be used in the manufacture of the influenza virus vaccine that will be administered in the fall. Currently, licensed vaccines contain three virus strains representing the strains predicted to be in U.S. circulation, as recommended by the U.S. Public Health Service (PHS) [including FDA, CDC, National Institutes of Health (NIH), and National Vaccine Program] for incorporation into the vaccine for 2004-2005. Because of the necessity to have a vaccine that matches the virus strains currently in circulation, vaccines manufactured for the previous year cannot be used.

FDA works closely to facilitate the rapid production of influenza vaccine each year. As soon as the strains are recommended, manufacturers begin to grow the virus strains in fertile hen's eggs. These strains of vaccine, known as "seed strains," used by each manufacturer are tested by FDA's CBER to assure they are the same as the recommended strains. FDA and manufacturers conduct tests to assure the safety and efficacy of the vaccine. Manufacturers submit the results of their testing along with sample vials from each lot to CBER for our "lot release." Because of the complexity of the manufacturing process, CBER performs "lot release" on each lot of influenza vaccine manufactured prior to distribution of the product. "Lot release" consists of CBER's review of the

manufacturers' test results, including tests on the lots of monovalent virus strains. Furthermore, to assure the safety and efficacy of these products, CBER performs additional testing as appropriate.

Although the manufacturing process and lot release is completed for some lots of influenza vaccine as early as July, the manufacturing of additional lots continues until September-October in order to manufacture and complete the testing on a very large number of vaccine doses. There has been a very significant increase in production over the past decade, as compared with approximately 20 million doses per year distributed in the mid-1980s. Because of the fragile infrastructure and decision of manufacturers to leave the market, the burden of production capacity and supply of influenza vaccine rested with thee manufacturers for the 2004-05 flu season. Chiron Corporation (Evans Vaccines Ltd.) manufactures Fluvirin, and Aventis Pasteur, Inc. manufactures Fluzone; both of these vaccines are inactivated influenza vaccines. MedImmune, Inc. manufactures FluMist, a live attenuated influenza vaccine.

2004-05 Flu Season

The loss of Chiron influenza vaccine supply remains a challenge. As you know, we are working hard to assure the safety and health of Americans as the flu season approaches. In coordination with other elements of the Department of

Health and Human Services (HHS or the Department), we have been actively exploring all viable options to secure additional dosages of flu vaccine licensed for use in the U.S. that will provide more Americans protection against the flu. As a result of these efforts, I can report that we have been able to increase the available supply of flu vaccines for the U.S. population to 61 million doses for this flu season.

Coupled with that initiative, we have been contacting manufacturers worldwide in an effort to identify increased supplies of antiviral medications that will provide further protection and treatment for Americans during this flu season and are making progress in this area as well. In addition, we have already been working with our partners in the United Kingdom as well as with Chiron Corporation to complete our review of the problems encountered at their production facility in order to expeditiously determine what steps would be required to bring that facility into compliance.

As a matter of enforcement policy, FDA inspects U.S. licensed vaccine manufacturing facilities every two years. Based on this schedule, FDA inspected the Liverpool, U.K. facility where the Chiron vaccine is produced in 1999, 2001, and 2003. It should be noted that Chiron acquired the facility in July 2003 after FDA conducted the biennial inspection. During the 1999 inspection, FDA identified various concerns and, as a result, issued a warning letter regarding the Liverpool facility. The most significant issues identified in 1999

inspection were the lack of validation for its manufacturing processes, including establishing proper limits for bioburden (including bacteria) and issues related to assuring sterility in the manufacturing process. During the 2001 and 2003 inspections, although FDA found that the company made improvements, we also made observations related to current Good Manufacturing Practices (cGMPs). In each case, FDA reviewed the corrective measures and plans in response to these deficiencies. If fully implemented, the company's plans appeared adequate to correct deficiencies identified at the facility.

It is important to understand that, from the start of the manufacturing cycle, influenza vaccine manufacturing is not a sterile process because it involves the use of eggs, which are not sterile. Therefore, a certain amount of bioburden will be present in early stages of manufacturing. However, vaccine manufacturers must have effective measures, such as sterile filtration, to eliminate this bioburden. As a further safeguard, FDA requires a lot release and testing system for vaccines. This is a vital component of the multi-step safety assurance process for vaccines. It is also important to understand that new flu vaccine is formulated and produced for each flu season, so that concerns identified with vaccine from the prior year's supply do not necessarily relate to the current year's vaccine supply.

FDA's 2004 Communications with Chiron and MHRA

On August 25, 2004, Chiron informed FDA that the company had discovered bacterial contamination in eight lots of final vaccine product for this year's flu season supply and advised that they were investigating the problem. They shared with FDA an overview of their planned investigation to determine root causes of the problem as well as their plan to retest all other lots produced. Chiron quarantined all influenza vaccine lots during its investigation, including those that had passed all required testing, and did not release any of the product.

In September 2004, FDA, CDC and Chiron scheduled weekly conference calls to discuss the status of the firm's investigation. Chiron stated to FDA that the company had identified the cause of the contamination and that the contamination was confined to the identified vaccine lots. The company indicated to FDA that it believed the cause of contamination in these lots could be traced back to one of two contaminated bulk lots used to formulate these final lots. Nonetheless, FDA concurred with the need for Chiron to thoroughly retest all final lots, complete a thorough investigation of the manufacturing process and provide a complete investigation report to FDA. While the investigation was ongoing, Chiron informed FDA that results of the retesting were negative and that the company would submit its final investigative report to FDA during the week of October 4-8.

In late September, Chiron advised that it would substantially meet its plans to supply influenza vaccine to the U.S. On September 28, Chiron's CEO affirmed this in testimony to the Senate Special Committee on Aging when he stated: "As of September 27th, it remains Chiron's expectation that between 46 million and 48 million Fluvirin doses will be delivered to the U.S. market beginning in early October as compared to the 50 million doses projected in July."

MHRA's October 5, 2004 Announcement

On the morning of October 5, 2004, MHRA announced a three-month suspension of Chiron's license to manufacture influenza vaccine. FDA had no prior knowledge of the MHRA's intention to suspend the firm's U.K. license. MHRA's Chief Executive, Professor Kent Woods, indicated that MHRA did not have the legal authority to notify FDA about the suspension announced on October 5 until after MHRA instituted its administrative action. Dr. Woods has also stated that, "Contrary to some reported statements, MHRA, as the responsible regulatory authority in the United Kingdom, made the decision to suspend Chiron's license after an internal meeting on October 4 and first informed the company and the FDA of this decision on October 5. At the same time, we informed other drug regulatory authorities via an intergovernmental rapid information alert."

Upon learning of the MHRA's suspension on October 5, 2004, FDA communicated with both Chiron and the MHRA. While Chiron indicated to FDA

that it believed it had satisfactorily addressed MHRA's inspectional findings and provided to FDA a copy of those findings and the company's response, MHRA expressed serious concerns about Chiron's vaccine stocks and the company's ability to assure the safety of the vaccine.

FDA Officials Dispatched to the U.K.

FDA dispatched a senior team of scientists, led by Dr. Jesse Goodman, the Director of FDA's CBER, to the U.K. on Wednesday, October 6, 2004, to gain further understanding of the MHRA's action. The team met with the MHRA on October 7, and met with Chiron on October 8.

FDA inspected Chiron's Liverpool manufacturing facility from October 10 through October 15, to evaluate the company's efforts to test for and assess the bacterial contamination detected in nine of the one hundred final vial lots of its influenza vaccine. FDA also evaluated Chiron's determination that the risk of bacterial contamination was confined to specific lots.

On October 15, 2004, upon completion of its inspection, FDA determined that it could not adequately assure that Chiron's vaccine met our safety standards. On October 15, we also provided Chiron with our inspectional observations (Form FDA 483) from our inspection and met with the company to discuss its compliance issues. FDA will continue to work with Chiron and the U.K. government to ensure that the company corrects the deficiencies in the Liverpool

plant so that it can eventually resume production of a safe and effective influenza vaccine. In the wake of the October 2004 inspection, FDA will work closely with MHRA and Chiron to assess any proposed corrective measures that the company submits in response to the October inspection and the company's findings of contamination in final lots. FDA will analyze Chiron's responses for their thoroughness, accuracy, and their adequacy. Ultimately, however, the agency's final determination regarding the effectiveness of Chiron's corrective measures will be based on a comprehensive inspection that we anticipate will occur once the company has notified the agency in February or March 2005 of the proposed corrective measure.

FDA's Response to the Flu Vaccine Shortage

Assuring the safety and effectiveness of vaccines is central to FDA's mission. Our goal is to assist the health care community as they work to provide protection to more Americans against the flu. To assist in these efforts, both Aventis Pasteur and MedImmune have indicated to FDA that they will provide additional doses of influenza vaccine. As a result, we have increased the available supply of licensed flu vaccine for the U.S. population to 61 million doses for this flu season, Aventis Pasteur will produce a total of 58 million doses of Fluzone and MedImmune has scaled up production to produce a total of 3 million doses of FluMist. FluMist is recommended for healthy individuals 5 to 49 years of age, and therefore, provides an option for those who would not receive

vaccine under CDC's priority guidelines as well as for certain categories within the CDC guidelines.

In addition to supplies of vaccine approved for use in the U.S., we have also identified about five million doses of influenza vaccine from foreign manufacturers that could potentially be available under investigational new drug applications (INDs). We have sent FDA inspectors to the manufacturing facilities of GlaxoSmithKline (GSK) in Germany and ID Biomedical in Canada to evaluate their manufacturing processes. These efforts could result in as much as 4 million doses from GSK and up to 1 million doses from ID Biomedical. Finally, in an effort to expand further the supply of vaccine to those with the greatest need, Secretary Thompson recently announced that military personnel will use FluMist and Defense agencies will redirect their supply of injectable vaccine to the high-risk population in the U.S. While this is essentially true, we are allowing DHHS to purchase 200,000 doses of injectable vaccine that we had contracted for and we are changing our plans to maximize the use of the intranasal FluMist. We are not, however, redirecting our remaining injectable vaccine to the US high risk population-- only the 200,000 doses."

We have also been contacting manufacturers worldwide in an effort to identify increased supplies of antiviral medications. Antiviral medications are drugs that are approved to reduce symptoms and in some cases prevent onset of influenza if taken early after exposure has occurred. These drugs will help protect and

treat for Americans during this flu season, and we are making progress in this area as well. There are enough antiviral medicines to treat influenza in 40 million Americans, if necessary.

To address the complications of those who experience the flu, Merck & Company plans to triple its production of pneumococcal polysaccharide vaccine from 6 million to between 17 and 18 million doses. Pneumococcal pneumonia is one of the most important and common serious complications of influenza, and the availability of this expanded supply during the current flu season will allow public health officials to lessen the possibility of this complication.

Preparations for Next Year

Aventis Pasteur believes they have the capability of producing the same or more doses of influenza vaccine for the 2005-06 flu season. In addition, MedImmune has indicated that it has the capability to produce 10 million doses of FluMist for the 2005-06 flu season and as much as 40 million doses by 2007.

We will continue to work with Chiron Corporation, in close collaboration with the UK regulatory authorities, to help Chiron address, as quickly as possible, the manufacturing problems they experienced during this year's production process. To this end, we have reached agreements with Chiron that allows for full sharing of information between the FDA and the MHRA as the company works to resolve the problems in Liverpool. In addition, FDA has also been encouraging foreign

licensed manufacturers to apply for U.S. licensure, and is providing clear pathways to efficiently reach this goal.

Looking to the Future

Immediately upon coming to HHS, Secretary Thompson under the leadership of President Bush began transforming the flu marketplace by investing in new technologies, securing more vaccines and medicines, and preparing stronger response plans. The largest investments ever made by the federal government in protecting against the flu have been made under President Bush's leadership.

In keeping with these unprecedented investments, we must move science forward to help create more efficient ways to produce flu vaccine so we have greater flexibility to deal with shortages or unexpected problems. In each of the past two budgets, the Department has requested $100 million to shift vaccine development to new cell-culture technologies, as well as to provide for year-round availability of eggs for egg-based vaccine. We received $50 million in the FY04 budget for this activity and urge Congress to fully fund the $100 million request in FY05 budget.

To help manufacturers overcome challenges such as the vaccine development problems Chiron is experiencing, FDA has been investing its energy and resources in important initiatives such as the Current Good Manufacturing Practices for the 21st Century (known as the cGMP initiative).

Under the cGMP initiative, FDA is working with industry to encourage the use of advanced technologies as well as quality systems and risk-based approaches that build quality into the manufacturing process. FDA is also using the same quality systems and risk-based approaches to modernize our manufacturing regulatory responsibilities. For example, we are providing advanced training for manufacturing investigators. This has led to greater inspection consistency and the ability to more readily identify manufacturing deficiencies. The cGMP initiative is also promoting better communication between manufacturers and the agency, which will enable manufacturers to anticipate and overcome production problems before they occur. Among the lessons we have learned from this year's events at Chiron is the need to enhance our international regulatory collaboration and harmonization efforts.

In the past year, we completed information sharing agreements with the European Medicines Agency, Health Canada, and SwissMedic, and most recently MHRA, to help assure that legal barriers do not inhibit critical communication between these agencies and FDA. FDA is undertaking an inventory of foreign manufacturing of U.S.-licensed products, such as flu vaccine, that are critical to public health, and will put into place information sharing agreements with other national regulatory authorities as needed. In addition, we recognize that public health needs and resources are increasingly global in nature and, in the hope that vaccines can be licensed in multiple regions of the

world, FDA has been encouraging more internationally harmonized product development.

Recent events have highlighted how imperative it is that we support the U.S. and global vaccine manufacturing infrastructures and invest in more efficient, reliable and modern methods for producing influenza vaccine. With adequate supply and inoculation, influenza is manageable and we will be more likely to successfully face the challenge of future pandemics.

Once again, thank you for the opportunity to come here today and testify on this very important issue.

I would be happy to respond to any questions that members of the Committee may have for me.

The CHAIRMAN. Now, let us turn to Mitchell Cohen. Dr. Cohen is director of the Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention. Welcome to the committee.

STATEMENT OF MITCHELL L. COHEN, M.D., DIRECTOR, COORDINATING CENTER FOR INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ATLANTA, GA

Dr. COHEN. Thank you. Chairman Craig, Senator Kohl, I am pleased to be here today to discuss CDC's efforts to address the current influenza vaccine shortage.

I thank the committee for your continued interest in influenza, an important public health issue affecting our nation as a whole and our nation's elderly in particular. Influenza is a contagious respiratory disease that can cause mild to severe illness and at times can lead to death.

While most healthy people recover from the flu without complications, some people, such as older people, young children, and people with certain health conditions, are at high risk for serious complications from the flu. Each year, influenza causes more than 200,000 hospitalizations and an estimated 36,000 deaths. Many of those deaths occur among the elderly.

Vaccination is the primary strategy for protecting individuals who are at greatest risk for serious complications and death. In the face of this season's influenza vaccine shortage, CDC, State and local health officials, practitioners, and vaccine manufacturers have worked tirelessly to protect our most vulnerable populations. We deeply appreciate the cooperation and the collaboration of all those who have helped to meet this challenge.

We also want to express sincere appreciation to the many people across the country who have made a sacrifice and stepped aside and not gotten their vaccine so that the limited doses of vaccines could be given to those at highest risk. Despite those concerted efforts, we cannot guarantee that all persons in the targeted high-risk groups will receive vaccine this year.

In general, CDC's efforts have concentrated on increasing vaccination coverage levels, increasing public demand for vaccine, increasing vaccine supply from domestic vendors, and improving core and developing innovative public health strategies.

Given the current shortage of influenza vaccine, our No. 1 objective this year is to ensure vaccination of the groups at greatest risk, although our long-term goal is to ensure a stable annual supply of influenza vaccine for all people who want it and to encourage more people to want it.

Current reports indicate that influenza activity in the United States has been low in comparison with last year, when influenza activity began early in the fall and resulted in more widespread outbreaks earlier in the season than usual. However, it is impossible to predict the level of influenza activity even at this point in the year. We must remain vigilant in our monitoring of the situation.

When on October 5, CDC learned that almost half of the nation's inactivated influenza vaccine supply would not be available for the

flu season, we began activities to address the situation through established public health actions and instituting innovative strategies. For example, CDC took immediate steps to work with partners to target the distribution of the remaining inactivated vaccine toward the most vulnerable populations; to identify available vaccine from other countries that might be used this season; to develop recommendations for the use of antiviral medications during the season and increase the agency's stockpile of these medications; to increase surveillance for influenza disease and outbreaks to provide early warnings of hot spots and perhaps to target our response; to develop and disseminate strategic communication messages to facilitate the public health response to the vaccine shortage and to inform the public of ways to reduce the transmission and severity of disease; and to assess the effectiveness of the strategies to target vaccine to high-risk groups and the response to influenza outbreaks. My written statement provides additional details of these and other of CDC's actions.

I would be remiss, however, to discuss influenza without mentioning pandemic influenza. Influenza pandemics are uncommon events. There have been three in the 20th century and their timing cannot be predicted. However, pandemic preparedness is a public health priority because of the potential to cause substantial numbers of deaths and tremendous social disruption over a very short period of time. In a large measure, current preparedness efforts are responsive to growing concerns about a very large avian influenza epizootic in Asia that has involved poultry, wild birds, and mammals. Importantly, much of what we are doing now in this challenging flu season to deal with this influenza shortage will help in our preparedness for the inevitable pandemic that will occur.

Flu has been and will remain a serious concern to the health and well-being of all Americans, but particularly older Americans. CDC, along with the other Department of Health and Human Services agencies, looks forward to working with Congress on the future opportunities to strengthen the fragile vaccine system which protects our nation's health.

This concludes my opening remarks and I will be happy to answer any questions that you have.

The CHAIRMAN. Thank you both very much.

[The prepared statement of Dr. Cohen follows:]

Testimony
Before the Special Committee on Aging
United States Senate

CDC's Influenza Vaccine Efforts

Statement of
Mitchell L. Cohen, M.D.
Director
Coordinating Center for Infectious Diseases
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 2:30PM
Tuesday, October 16, 2004

Mr. Chairman and members of the committee, I am pleased to be here today to discuss the Centers for Disease Control and Prevention's (CDC) efforts to address the current influenza vaccine shortage. Vaccination is the primary strategy for protecting individuals who are at greatest risk of serious complications and death from influenza. In the face of this season's influenza vaccine shortage, CDC, state and local public health practitioners, and vaccine manufacturers have worked tirelessly to protect our most vulnerable populations. I want to especially recognize the good faith, cooperation, and the significant contribution of Aventis Pasteur to ensure that the available supply of influenza vaccine goes to those people who truly need it most this season. And we must not forget the important service of immunization providers on the front lines in doctors' offices, health clinics, grocery stores, and pharmacies working to prioritize, deliver, and administer vaccine so that it reaches high-risk individuals.

I also want to thank the nation's health protection heroes, those people across the country who are stepping aside and not getting vaccinated so that those at high-risk will be protected this influenza season. I particularly appreciate the cooperative and collaborative spirit of Americans who have pulled together to help us meet this challenge head on.

I would be remiss, however, if I failed to mention the tremendous progress we have made. In the last four years, the Department of Health and Human Services has begun investing in new technologies, securing more vaccines and

medicines, and preparing stronger response plans. We have made significant investments in protecting against the flu, including increases for CDC influenza funding ($17.2 million to $41.6 million, 242%) and creation of Strategic Reserves/Stockpiles ($0 to $80 million). These investments are further detailed as follows:

- **New Technologies:** In each of the last two budgets, HHS has asked for $100 million to shift vaccine development from the cumbersome egg-based production to new cell-culture technologies, as well as to provide for year-round availability of eggs to provide for a secure supply and surge capacity. These new technologies will help produce flu vaccine more efficiently and provide more adaptability to unexpected problems or losses in production.

- **Creating the Nation's First Stockpiles of Medicines:** For the first time ever, we have created stockpiles of both influenza vaccine and antiviral medications. The Department invested $40 million in 2004, and is planning to invest another $40 million in 2005, to stockpile influenza vaccine through the Vaccines for Children Program. We invested $87.1 million to stockpile 2.3 million doses of Tamiflu; we invested $34 million on Rimantadine capsules to treat 4.25 million adults and on Rimantadine syrup to treat 750,000 kids. These stockpiles give the government new

ability to protect the most vulnerable, and respond effectively when there is a shortage of vaccine.

- **Pandemic Flu Plan:** In August, Secretary Thompson unveiled the department's draft Pandemic Influenza Response and Preparedness Plan. This plan outlines a coordinated national strategy to prepare for and respond to a flu pandemic. One of the first internal committees the Secretary created when he came to HHS was on the pandemic flu.

- **Improving Access by Covering Costs:** The Centers for Medicare & Medicaid Services (CMS) has more than doubled the payment rates for the vaccine and its administration since 2000. In 2004, CMS is paying $18.30 for the vaccine and administration -- up from $8.92 in 2000. This is helping to ensure the vaccine is affordable for patients to get and cost-effective for providers to administer.

PREPARATIONS FOR THE 2004-05 INFLUENZA SEASON

Currently, three vaccine manufacturers are licensed to produce influenza vaccine for use in the United States; two produce inactivated vaccine delivered by intramuscular injection and one makes a live vaccine delivered by nasal spray. The inactivated vaccine, commonly referred to as the "flu shot," represents the majority of influenza vaccine available in the United States and is licensed for use in all individuals 6 months of age and older. The nasal spray vaccine is a

new vaccine, introduced to the U.S. market for the 2003-04 influenza season, and is licensed for use in healthy persons between 5 to 49 years of age. All influenza vaccine is produced, and the vast majority is distributed and administered, by the private sector. Because of the time required to obtain adequate supplies of eggs in which influenza virus is grown, manufacturers must predict demand and decide how much of the vaccine to produce six to nine months before the influenza season begins. Because influenza vaccine production is a complicated process involving several steps over a long period of time, it was not possible to begin new production of influenza vaccine after the shortage was announced.

CDC and the Department of Health and Human Services (DHHS) took several steps to prepare for the 2004-05 influenza season, including specific action to prevent a late-season surge in vaccine demand such as the one experienced last year in which the demand for influenza vaccine in the United States exceeded what had been experienced in previous influenza seasons. In preparation for the 2004-05 influenza season:

- Vaccine manufacturers licensed to produce influenza vaccine for the U.S. market anticipated producing a supply of approximately 100 million doses of inactivated influenza vaccine for this year, significantly more doses than have ever been produced for the United States.

- CDC planned to establish a stockpile of 4.5 million doses of influenza vaccine for the nation's children. The primary purpose of the stockpile was to meet late-season, unmet pediatric demand as we are currently experiencing this year.

- CDC augmented domestic influenza surveillance this season with surveillance for pediatric hospitalizations and pediatric mortality reporting. In addition, CDC is expanding its capacity for rapid detection of new strains of influenza viruses and has funded a study to prospectively evaluate vaccine effectiveness during this winter's influenza season.

As noted previously, DHHS is supporting activities designed to ensure year round influenza vaccine capacity and to incentivize the accelerated development, licensing and domestic production of cell-culture influenza vaccines. The President's FY 2004 and FY 2005 budgets each proposed $100 million for these efforts. A contract for egg surge capacity worth about $10 million has already been awarded. Negotiations are currently underway for tissue culture vaccine research and development contracts.

In addition, DHHS has expanded biosurveillance activities so that scientists can more rapidly detect changes in circulating influenza viruses and determine potential strains for vaccines. DHHS is collaborating with the Department of

Agriculture and the Department of State to further enhance surveillance efforts in Asia, in both human and animal populations

CDC RESPONSE TO THE 2004-05 INFLUENZA VACCINE SHORTAGE

On October 5, 2004, Chiron Corporation notified DHHS that none of its influenza vaccine (Fluvirin®) would be available for distribution in the United States for the 2004–05 influenza season. The company indicated that the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom, where Chiron's Fluvirin vaccine is produced, suspended the company's license to manufacture Fluvirin vaccine in its Liverpool facility for three months. This action prevented the release of its vaccine for this influenza season. This action reduced by approximately 46 to 48 million doses, or almost one-half, the expected supply of inactivated influenza vaccine available in the United States for the 2004–05 influenza season.

Following the Chiron announcement, DHHS and its agencies, including CDC, took immediate action in response to the loss of this vaccine supply. CDC responded quickly and effectively to the influenza vaccine shortage by activating the Director's Emergency Operations Center (DEOC) Influenza Task Force to coordinate the overall CDC response. CDC's immunization, infectious disease, and other experts are working collaboratively across the agency to address areas such as clinician policy and guidelines, vaccine supply and distribution,

healthcare impact, logistics, influenza assessment and surveillance, informatics, and communications. These dedicated public health professionals have worked tirelessly to protect the nation's health during this influenza vaccine shortage.

CDC is working hard to target the distribution of the remaining inactivated vaccine towards the most vulnerable populations; identify available vaccine from other countries that might be used this season; reinforce the agency's supply of antiviral medications in the Strategic National Stockpile and provide recommendations for their use during this influenza season; develop strategic communication messages to facilitate the public health response to the shortage; enhance surveillance for influenza disease and outbreaks so that early, effective responses can be delivered; and implement a comprehensive monitoring and evaluation system to assess the effectiveness of the strategies to target vaccine to high-risk groups and the response to influenza outbreaks.

Interim Influenza Vaccination Recommendations for the 2004-05 Season

On October 5, in coordination with the Advisory Committee on Immunization Practices (ACIP), CDC issued interim recommendations for influenza vaccination during the 2004-05 season. The interim recommendations identify the priority groups of people that should receive the limited supply. These include people who are most vulnerable to develop serious complications and even death from influenza: adults 65 years of age and older, children 6 to 23 months of age, individuals with certain chronic underlying medical conditions, pregnant women,

residents of nursing homes and long-term care facilities, and children on chronic aspirin therapy. In addition, the ACIP recommended vaccination for individuals who might otherwise spread influenza to high-risk individuals, including household contacts of infants under 6 months of age and healthcare workers providing direct, hands-on patient care. These interim recommendations take precedence over earlier recommendations.

Influenza Vaccine Supply and Allocation Plan

Following the Chiron withdrawal, Aventis Pasteur announced that it would work with CDC to develop a plan to target the remaining available influenza vaccine toward providers serving the populations at greatest risk for serous complications from influenza. I commend Aventis Pasteur for its leadership and willingness to join us in addressing this public health concern. In addition, state and local health officials have worked together with the CDC and Aventis Pasteur to assure the most equitable and efficient means of distribution of the remaining, limited supply of vaccine across the Nation. The significant contributions and leadership of these public health professionals has enabled our nation to respond effectively to this public health challenge.

As of October 5, Aventis Pasteur had planned to produce over 50 million doses of inactivated influenza vaccine for the 2004-05 influenza season. At that time, approximately 33 million doses had already been shipped to pediatricians, primary care and other office-based physicians, public health providers, and

other community-based vaccine providers. Approximately 14.2 million of the remaining 22.4 million doses of unshipped vaccine were allocated for redistribution through Aventis Pasteur contracts with providers serving the high-priority populations. On October 19, 2004, Aventis Pasteur announced that it would produce an additional 2.6 million doses of vaccine that would be available in January 2005. With these additional doses, their total of inactivated influenza vaccine for this season is expected to exceed 58 million doses, of which 10.3 million are still to be produced and distributed in the coming weeks, as of November 9, 2004.

CDC and Aventis worked to identify a number of orders placed with Aventis Pasteur and the seven distributors through which Chiron vaccine is shipped, that were intended for providers known to serve substantial numbers of high-risk patients. These included doses ordered by:

- State and local health departments;
- The Vaccines for Children Program;
- Children's providers;
- Healthcare providers for Aventis Pasteur's preservative-free influenza vaccine (licensed for use with children 6-35 months of age);
- The Department of Veterans Affairs and the Indian Health Service;
- Long-term care facilities and acute care hospitals;
- The Visiting Nurses Association of American (VNAA); and
- The Department of Defense.

Every effort has been made to provide vaccine to as many providers serving high-risk populations as possible in a timely fashion.

CDC, state and local health officials, Aventis Pasteur, and Chiron vaccine distributors worked together to canvass the orders placed with the seven Chiron distributors, with an emphasis on orders placed by providers likely to be serving a high number of priority patients; and surveyed long-term care facilities to identify those facilities that ordered Chiron vaccine, either directly or via a sub-distributor or intermediaries such as pharmacies.

The CDC implemented a secure web-based application, the Flu Vaccine Finder that is available to state health officials to identify all doses of inactivated influenza vaccine shipped to their state during the 2004-05 season. State health officials and CDC have worked together, in consultation with local health departments, to develop a formula for the equitable distribution of the remaining influenza vaccine to be shipped. This formula took into account the population of high-risk individuals in each state and the number of influenza vaccine doses that have already been shipped to each state.

Of the limited number of licensed doses of vaccine that remains to be shipped, there is agreement that all public sector orders that were submitted on federal, state, and multistate contracts will be filled. CDC estimates this to be

approximately 11.9 million doses total, with 3.4 million of those doses to complete the public sector orders that were submitted on federal, state and multistate contracts. CDC has asked state health officials to work collaboratively with local health departments and private immunization providers to guide the final allocation of the remaining approximately 7.2 million adult doses. State and local health officials are best suited to develop and implement this second phase of the vaccine allocation plan. Another 1.2 million doses of pediatric vaccine will be allocated to states using the same approach. State and local health officials have the most accurate and comprehensive understanding of the needs within their jurisdictions, the necessary relationships with public and private health care providers to target vaccine to reach the most vulnerable populations in their states, and the authority to ration in times of shortage.

Price Gouging

Finally, there is the issue of alleged price gouging. CDC is very concerned to learn of reported incidences of price gouging during this particularly challenging time. In response to the reports of alleged price gouging, the Secretary sent a letter on October 14, 2004, to each state urging them to thoroughly investigate reports of price gouging involving influenza vaccine and to prosecute to the full extent of the law those found to be involved. CDC is also collecting reports on price gouging and sharing them with the National Association of Attorneys General and state prosecutors.

Additional Sources of Influenza Vaccine

Approximately 3 million doses of the intranasally administered, live, attenuated influenza vaccine, FluMist, are being produced for the 2004-05 season. This vaccine is encouraged for use among healthy persons ages 5–49 years who are not pregnant. This includes healthcare workers (except those who work with severely immunocompromised patients in special care units) and household contacts of infants less than 6 months of age. CDC is making people aware of this alternative to inactivated influenza vaccine.

Several manufacturers of influenza vaccines licensed for use in Europe and Canada have vaccine, which is under review for use in the United States as Investigational New Drugs (IND). Because these vaccines are not currently licensed in this country, they will have to be administered under special protocols with written consent. CDC is studying the feasibility of use of IND vaccine as it is developing protocols for vaccine use and the U.S. Food and Drug Administration (FDA) is inspecting the manufacturing plants. As many as 5 to 6 million doses of vaccine may be available from these manufacturers, although even if approved for an IND, we would not expect delivery of most of this vaccine until December and January.

Antiviral Medications and Pneumococcal Vaccine

Influenza antiviral medications are an important adjunct to influenza vaccine in the prevention and treatment of influenza. CDC has developed interim

recommendations on the use of antiviral medications for the 2004-05 influenza season. The interim recommendations were developed to reduce the impact of influenza on persons at high risk for developing severe complications secondary to infection. The recommendations are not intended to guide the use of these medications in other situations, such as outbreaks of avian influenza.
Influenza antiviral medications have long been used to limit the spread and impact of institutional influenza outbreaks. They are also used for treatment and chemoprophylaxis (prevention) of influenza in other settings. In the United States, four antiviral medications -- amantadine, rimantadine, oseltamivir, and zanamivir -- are approved for treatment of influenza. When used for treatment within the first two days of illness, all four medications are similarly effective in reducing the duration of illness caused by Strain A influenzas by one or two days. Only three antiviral medications (amantadine, rimantadine, and oseltamivir) are approved for prevention of influenza.

CDC encourages the use of amantadine or rimantadine for prevention and use of oseltamivir or zanamivir for treatment of those who are ill from influenza, as supplies allow. People who are at high risk of serious complications from influenza may benefit most from antiviral medications.

The United States has a supply of influenza antiviral medications for both adults and children stored in the Strategic National Stockpile for emergency situations. There are 1,336,380 regimens of rimantadine tablets, 60,000 regimens of

rimantadine syrup, 859,993 regimens of oseltamavir capsules, and 110,336 regimens of oseltamavir suspension. DHHS has procured additional supplies of antiviral medications, and shipments are arriving weekly. By the end of December, the federal stockpile of antiviral drugs will include enough doses of rimantadine for 4.25 million adults and 750,000 children and enough oseltamivir for 2.3 million people. Rimantadine will be made available to states and territories for use in outbreak settings, as might occur in a hospital or long-term care facility, if commercially available supplies become depleted nationwide. Because oseltamavir is the only antiviral drug known to be effective against avian influenza, we will work to maintain the supply of oseltamavir in reserve to be used in the event of an influenza pandemic.

In addition, Merck & Co. is tripling its production of pneumococcal vaccine used to prevent pneumococcal disease, which is a common complication of influenza. Pneumovax is not a substitute for the influenza vaccine, but can help prevent influenza complications. Many people who fall into the priority groups for the influenza vaccine should also get the pneumonia vaccine.

Communicating the Public Health Response

Since the release of the interim influenza vaccination recommendations, CDC has used a variety of channels to communicate comprehensive information about the influenza season, the recommendations for priority groups for vaccination, the status of the vaccine supply, and alternative methods of reducing the

transmission and severity of disease. Relevant and timely communications with the public, health care professionals and policy makers is a critical component of the public health response to the current influenza season and the vaccine shortage.

CDC's influenza web portal (http://www.cdc.gov/flu) features updated information and materials for the public and clinicians. Materials are available in ten languages (in addition to English) as well as in low-literacy formats. As the public health response to the vaccine shortage has evolved, this website has become a vital resource receiving 300,000 visits per day at its peak, leveling off at over 150,000 visits per day over the past few weeks.

In addition to communications via the Internet, CDC established a new toll-free hotline number, 1-800-CDC INFO, to respond to public and clinician inquiries related to the influenza season and the vaccine shortage. This automated hotline includes selections in English and Spanish, and provides callers with timely and relevant information regarding the influenza season and the vaccine shortage. Since the announcement by Chiron on October 5, 2004, CDC has responded to several thousand inquiries from the public and clinicians through its hotlines.

In collaboration with the non-profit Ad Council, CDC recorded and distributed two audio public service announcements to over 9,000 AM and FM radio stations

across the nation. In addition, two video public service announcements are being developed for distribution before Thanksgiving, and plans are underway to run print ads and articles in the nation's newspapers over the next several weeks.

CDC has also made specific efforts to reach business and educational institutions with critical information about the priority populations recommended for vaccination and alternative methods for preventing transmission of disease in the workplace and educational settings.

THE 2004-05 INFLUENZA SEASON

Influenza seasons are unpredictable. Although epidemics of influenza occur virtually all every year, the particular viruses and the beginning, peak, severity, and length of the epidemic can vary widely from year to year. Before a season begins, it is not possible to accurately predict what the season will look like. However, as of the week ending October 30, 2004, influenza activity in the United States has been low. Forty (0.8%) of 4,736 respiratory specimens tested by U.S. World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories were positive for influenza. The proportion of patient visits to sentinel providers for influenza-like illness (ILI) and the proportion of deaths attributed to pneumonia and influenza were below epidemic levels. One state has reported regional influenza activity,

one has reported local activity, and 26 states and New York City have reported sporadic influenza activity. Twenty states and the District of Columbia have reported no influenza activity.

CDC has characterized three influenza viruses collected by U.S. laboratories since October 1, 2004. All were influenza A (H3N2) viruses and were characterized as A/Fujian/411/2002-like, which is an influenza component included in the 2004-05 influenza vaccine.

CONCLUSION

Thank you for bringing additional attention to this important public health issue. CDC is committed to protecting and promoting health for all Americans, preventing disease and disability through public health research and public outreach, and support of important interventions including vaccination. Recognizing the important role of vaccines in protecting the health of all Americans and in preparing for future threats, we will continue to work with our partners to manage the current influenza vaccine shortage and to address our nation's need for access to a safe, reliable supply of influenza vaccine in the future.

Thank you for your interest in this issue and your support of CDC's immunization programs. I will be happy to answer any questions.

The Chairman. Let us proceed with questions, and again, we thank you for being here.

Dr. Crawford, it has been reported that millions of doses of Chiron vaccine had to be destroyed, but there was doubt as to whether they had actually been contaminated. Could any of those doses have been saved? That would be my first question. Could you have tested the vaccines for safety? Is your regulatory system flexible enough to adapt the review process in the current situation?

Dr. CRAWFORD. The situation on the vaccine produced by Chiron Corporation in Liverpool, England, this year was the following. We were notified in August of some problems with the manufacturing process, which essentially means that you take a contaminated product that occurs because of what is called bioburden—and remember, the vaccine production comes from chicken eggs and they are not sterile and so that leads to a burden of bacteria that has to be reduced over time. They were having difficulty getting it reduced in 9 of 100 lots they were producing.

So we were notified that this was a problem. They were continuing to work with the nine lots, but it looked like they were beyond reclamation. So we went into a mode of consultation, we and the Centers for Disease Control and Prevention, and separate of the British government was doing the same kind of thing, a little bit later, but they were basically performing the same kind of operation.

At the end of the day, the British concluded on October 5, which was the final date on which the corporation was to report to the Food and Drug Administration what were the prospects for the entire production, the British concluded that they could not guarantee that contamination did not occur in the remaining 91 lots. We immediately dispatched a team and did one of the most in-depth inspections any government has ever done because we recognized that this would critically diminish our vaccine stores.

At the end of that time, I received a report and the essence of the report was that the nine vaccine lots in question are beyond reclamation and we cannot guarantee that the remaining 91 lots aren't incubating some contamination of some kind or another. Recognize that the bacteria that was found in these nine lots, which is a bacteria called Serratia marcescens, essentially is like a sentinel finding. In other words, if you find it, you know that there could be contamination across all of the lots of vaccine and certainly within that lot. Among the other kind of contaminants would be viruses that you can't detect, bacteria that have long incubation periods.

In short, there had been a breakdown in production, a systematic breakdown. So by the power vested to me, I had to make the conclusion that we could not guarantee the safety of any of the lots of vaccine and therefore ordered them not introduced into production here or anywhere else, for that matter.

The CHAIRMAN. So it is obvious your conclusion was that the balance, the 91, had a high risk of contamination?

Dr. CRAWFORD. Absolutely. Yes.

The CHAIRMAN. So it was obviously your opinion, then, that nothing could be salvaged from that?

Dr. CRAWFORD. That is correct.

The CHAIRMAN. Medical science or the technology of the laboratory today does not allow that kind of a determination on a lot-by-lot basis?

Dr. CRAWFORD. No, the—thank you for the question. Actually, what would have to happen is you would be taking something that was in all likelihood contaminated and you would be trying at the end of the process to decontaminate it. You would have to have something like either very strong antibiotics, and since antibiotics do not work against viruses and some of the other things we would be concerned about, you would have to have either chemical decontamination with a mercury-containing product or you could try cold filtration one more time.

But even at the end of that time, based on our mathematical models and the conclusions that we had drawn based on FDA's experience with these kind of things, we still could not assure the American people that if we gave this vaccine, there wouldn't be illness problems. It most likely would have been something like abscesses, but it could have been a systemic infection that could have been quite serious, indeed.

The CHAIRMAN. The process you are describing for us is, I think in all modern terms, an antiquated or an old process, is it not?

Dr. CRAWFORD. The process of the production of the vaccine——

The CHAIRMAN. That is what I am speaking of.

Dr. CRAWFORD [continuing]. Is decades old and it is a very old process. As I mentioned earlier, if I may——

The CHAIRMAN. Please.

Dr. CRAWFORD [continuing]. We do believe that we need to get away from this egg-based production facility—I mean——

The CHAIRMAN. To cell-based, is that not correct?

Dr. CRAWFORD [continuing]. To a cell-based operation which would produce the product starting from the beginning without this contamination. It just doesn't make any modern scientific or laboratory sense to start with a contaminated product which has this bioburden, as we call it, and then try to decontaminate it over the cycle of production. It is much better to have something more modern. These cell-based technologies for producing vaccine do exist, but the state of them are such that they can't get enough volume, not enough virus production to get it done.

The CHAIRMAN. My time has run out and I am pleased that we are joined by my colleague from Oregon. Ron, welcome. Before I turn to Ron for any opening comments, you were the first here. Would you like to ask questions, Herb, of this panel and then we will move to Ron?

Senator KOHL. OK. Thank you very much, Mr. Chairman.

Will you say again how many doses are available this year and how many would we normally need?

Dr. CRAWFORD. We have 61 million doses available this year. We had been shooting for 100 million doses for this vaccination season. This amount has been increasing considerably as we move, particularly as the Centers for Disease Control and Prevention moves to encourage Americans to get the vaccine. We would like to have—I think Dr. Cohen would want to speak to this, but we would like to have 100 million or more, but only about in the late 1990's, we were actually using about half of what we were projecting for this

year. But it is a good thing that we want to move to 100 million. We just weren't able to have them in the market this year.

Senator KOHL. I don't think I fully understand. We have 61 million doses available.

Dr. CRAWFORD. Yes.

Senator KOHL. How many did we use last year?

Dr. CRAWFORD. Dr. Cohen, will you——

Dr. Cohen. It was about 85 million doses last year. It is projected that in the United States, there is probably, under the previous guidelines, about 185 million people who would benefit from immunization. Now, without having anywhere near that amount of vaccine, we had to hone the recommendations to those people who were the most vulnerable. In doing that, it probably reduced the number of people for whom the vaccine would be indicated to about 90 million.

Now, as I had mentioned, it varies from different priority group to priority group what rate of immunization you achieve, but generally across the board, we only immunize less than 50 percent of the people for which the vaccine is recommended. So based on the figure of 90 million and knowing that less than 50 percent of people actually seek vaccine, we estimated that we would need between 42 and 50 million doses this year to meet what would be projected demand.

Senator KOHL. Well, if we have 61 million doses available and you are projecting a usage of maybe 50 million, so are you suggesting that based on previous records and usage in other years, the 61 million doses should cover most all of the people who will appear at a clinic for a dose?

Dr. COHEN. Well, there are actually several issues that come to play. One is that on October 5, when we found out about this, 33 million of those doses had already been distributed and we do not know how much of that vaccine was used in individuals who were not high-risk patients. So we don't know exactly how much of that amount of vaccine was available. So that is one of the things that confound that.

Also, the ability to move vaccine from an area in which there is a high need for it to an area where there is less need doesn't always work as well, so you have distribution problems that may make you unable to give vaccine to all of those people who really would be indicated to receive it.

Senator KOHL. I want to spend all my time just getting an understanding and clearing this up. In the last several years, is the dosage, the vaccine use, about 85 million?

Dr. COHEN. It has increased over the last several years and I think that is one of the things that——

Senator KOHL. What has been the number? Can we get a number? Does it vary between 75 and 80 million? Is that a fair assessment?

Dr. CRAWFORD. Yes, that is. Between 70 and 85 million is a fair——

Senator KOHL. Are you saying that we have 61 million flu shots available?

Dr. COHEN. That is correct.

Senator KOHL. So there is not—while there is a shortage, it is not as though 75 percent of the people who want or who are normally expected to get vaccinated won't be able to. It is more like 20 percent of the people who normally would show up for a vaccination conceivably may not get it if the requirements are comparable to what we have had in the last few years. Sixty-one million doses, 75 to 80 million requests in the last several years, so that is what we are talking about, is that right, Mr. Crawford?

Dr. CRAWFORD. That is correct. Additionally, because there is this shortage, we have engaged the companies that manufacture the antiviral medication that can be used both as a treatment for flu and as a prevention for flu and we have 40 million doses of that that have been committed by the companies from around the world that manufacture the pill.

Senator KOHL. One last question. FluMist, do we use FluMist now?

Dr. CRAWFORD. Yes, we do. It has been on the market since last year. They were not able to sell last year all of their production, so they scaled down to only two million doses this year, which is about what their market was last year, as I understand it, and they have now, since we have engaged them in discussion, they have been able to increase that to a total of three million doses for this year, and that is included in that 61 million total.

Senator KOHL. My last question, is FluMist as effective as vaccine?

Dr. CRAWFORD. Dr. Cohen? FDA approved it on the basis that—it is a modified live virus, not a killed virus. It is as effective, but it can only be used in healthy people between 5 and 49 years of age. Even if you are between 5 and 49 years of age and you have some disability that might affect the immunizing potential, such as diabetes or lack of immune competence or something like that, you should not be taking the FluMist vaccine. It is only for healthy people in that narrow age range.

Senator KOHL. Thank you, Mr. Chairman.

The CHAIRMAN. Herb, thank you.

Now let me turn to Senator Ron Wyden. Ron, if you would like to make an opening comment, fine, and then you can proceed with your questions.

Senator WYDEN. Mr. Chairman, thank you. I will spare you and them, our guests, any opening filibuster and just begin, if I might, with you, Dr. Crawford.

It seems to me getting good flu vaccine out to the American people is Public Health 101. The fact that it is not getting done is, to me, a signal that a significant part of our public health system is really dysfunctional. I want to just ask you a couple of questions because I am concerned not just about the crunch this winter, but the prospect that this will get repeated again and again if we don't have in place the kinds of policies to ensure that that is not the case.

When the number of flu vaccine companies producing vaccines for the United States fell to two, why didn't one of our many agencies in the government essentially say, "Look, we have got a coming crisis on our hands and bring the relevant people, the companies, independent scientists, consumer advocates, the relevant people in

to, in effect, put together a plan to make sure a shortage doesn't happen? They could give you their recommendations. Some might take legislation, some might not. Some might take money, some might not. But why didn't that happen in this case, because certainly there was an early warning that we were going to have this kind of situation. Tell me why, in your opinion, that didn't take place.

Dr. CRAWFORD. As you may know, we began that process early in this decade and the key event was a Congressional hearing in June 2002 on the fragility of the vaccine supply. I testified at that hearing and estimated that by this year, we probably would be down to one company wanting to do business in the American market and how that put us at an unbelievably vulnerable spot.

We began a process. That is where we asked for this $100 million to try to convert from the egg-based to the cell-based and Congress responded with half that amount and then a promise to try to do more as we needed it. So that effort is now beginning.

Also, the National Institutes of Health cranked up its research in flu vaccine production from apparently a small amount to about, I think it is $282 million per year this year. So the research started, but it takes, as you know, three to five years to get what you want, and what we want is to get away from that kind of production.

The other thing we talked about was how do we incentivize the industry in order to want to enter the market. I think we said that probably five producers of flu vaccine in the world by 2004. There actually now are six, but not all of them want to enter the U.S. market. The incentivization never was figured out at all.

We looked at our regulations and we believe these Good Manufacturing Practices, which is the method, as I mentioned, that we use to regulate the flu vaccine industry either here or wherever it is if they want to be in this market, can be streamlined and sophisticated. We have started on that process. We are not done with it. We are done with it for drugs and we should be done with it for vaccines next year.

But the middle part of it is what incentive is there for companies to enter this market, something FDA has little control over, but we did signal it in 2002.

Senator WYDEN. I think what concerns me is that if we use that model, if somebody comes to the Congress and says, "Well, there is going to be a problem, we need some money, and we ought to look at incentivization, as sure as the night follows the day, we are going to have this exact problem with respect to other vaccines, Doctor." That is not what I am talking about.

What I am talking about is why we don't have one agency as the point or lead to have the companies, scientists, and consumer groups say, "This is what we need and we need it within 90 days." I mean, we are capable in this country of going to war in a hurry. Well, this is a need for a domestic mobilization, and pardon me if I don't think somebody coming to the Congress and talking about incentivization and some money, I don't think it is a plan.

I am going to have further contacts with the agency about this because it just seems to me when you are dwindling down to where we are, it is going to take a lot more than coming up to a Congres-

sional committee, talking about some money and talking about some incentivization. To me, what I have just essentially outlined is also a way to hold the Congress accountable. To me, if the public health community, the companies, the scientists and consumer groups say, this is what we need, we need it within 90 days, and then the Congress and the executive branch don't act, then you know you can hold somebody accountable.

What you have described when everybody is off talking about incentivization doesn't strike me as a program.

Let me, if I might, ask you about one other area. The State of Illinois, the city of New York, and other States have purchased, as you know, a significant number of doses of flu vaccine from European distributors in the hope that they can bring the vaccines into the country and get them to the most vulnerable. The Governor of Illinois sent you all a letter in October of this year asking the agency what needs to be done. I understand you need data from the manufacturers, Aventis and GlaxoSmithKline. Are these companies cooperating with you at this point?

Dr. CRAWFORD. Yes. Just quickly on what you said earlier, we would welcome all the help we can get. Whatever FDA can do within its authority, we will try to do, but——

Senator WYDEN. Would FDA like to be the lead agency? I mean, what I just basically described is what amounts to a public health SWAT team.

Dr. CRAWFORD. Yes.

Senator WYDEN. When you see a problem, you essentially bring the relevant people and agencies and you put together the program, say we need it within 90 days, and if Senators like us then don't vote for it, you have somebody that you can go to and you know how to do it. Would FDA take the lead in what I just described?

Dr. CRAWFORD. Well, we would need to do it with CDC, who is here. Dr. Cohen is from CDC. So we would be a partnership. We have good diplomatic relations and we will work hard together.

Senator WYDEN. Dr. Cohen, do you want to go on record as saying you are interested in something along the lines of what I said, what amounts to, with FDA, what amounts to a public health SWAT team where, in effect, when you see a problem like we saw several years ago with flu vaccine, we take a different approach?

Dr. COHEN. I think that you are pointing out a very severe problem that has been recognized for almost the last decade, and it is not just flu vaccine.

Senator WYDEN. Right.

Dr. COHEN. We are in a very fragile circumstance for all our vaccines where we have one or two or three producers, and it relates to a whole variety of issues that have economic and other considerations as to why companies don't want to produce vaccines and we would be very happy to work and look at all the possible solutions to try to resolve this issue. It is an important public health problem.

Senator WYDEN. Let me then go the next step and flesh it out, but the fact that the two of you would be willing to have your agencies look at heading this up is constructive. Just so we are clear on the record, Dr. Crawford, with respect to those two companies

cooperating on the matter of getting the data, given the fact that we have got a significant number of cities and States, in effect, going out of their own volition, I am interested in whether this data has been forthcoming.

Dr. CRAWFORD. Yes. You are right. There are a number of Governors that have been able to find in distribution channels, generally wholesalers, a certain number of doses of vaccine. This amount could be up to as much as 750,000 doses. We are evaluating that. They were sold from these manufacturing facilities and have been in circulation for a while. We have to be sure they have been refrigerated correctly and also they were produced in a safe way. Then we have to figure out a plan for bringing them into the country. None of that has come into the country yet, but it is still available and we should have some action on that very shortly, indeed.

The other thing is that FDA has gone around and asked every known manufacturer around the world if they had spare doses. We have come up with approximately six million doses that we are in the final stages of evaluation. The manufacturers of those doses have been completely cooperative and we should be able, again, within a very short amount of time, to make a determination on them and hopefully some or all of that product could be here by the end of this year.

Senator WYDEN. One last question if I might, Mr. Chairman. I am just puzzled on one point. Has the agency contacted Glaxo specifically on this matter of documentation, Dr. Crawford?

Dr. CRAWFORD. Yes, we have.

Senator WYDEN. My understanding was that the agency had not. The reason I ask is that I was concerned that there had been some delay because my understanding was that FDA was waiting to decide to authorize this because they were waiting for CDC to give a recommendation or a direct authorization. But that is not your understanding?

Dr. COHEN. No. In fact, we have been working very closely with FDA and a number of these companies because this is not a licensed product in the United States and under current rules and regulations, this would have to be used as an investigational new drug. So we have been working very closely to handle all of those regulatory activities that are required to be able to bring the drug in and use it under those considerations.

Senator WYDEN. How long, gentlemen, will it take for these Governors and cities to get the approval to bring the vaccines into the United States that they want? How long is this going to take?

Dr. CRAWFORD. We are evaluating them as fast and as hard as we can. I can't really say, but we have been at it for a few days. Normally, we can make some determination within two to three weeks.

Senator WYDEN. So within two to three weeks, these Governors and mayors—I know the city of New York wants to do it—they ought to have an answer?

Dr. CRAWFORD. Yes, they should.

Senator WYDEN. Mr. Chairman, you have been very generous. If I could submit some additional questions in writing on this, it would be very helpful.

The CHAIRMAN. All right. Thank you.

Senator WYDEN. Thank you.

The CHAIRMAN. Ron has followed a line of questioning that I would like to pick up now for my second line because I think it is very important. I said early on in my opening statement, it appeared to me that the situation we are involved in is a liability issue, a licensure issue, and a stability of the market issue, a combination of all of those put together.

You have talked about the licensing process and I wish, Dr. Crawford, you would pursue that with me a little bit more. As you reach out to foreign companies, encouraging them to enter the market, are they refusing to? Is the market too complicated? Is the process too long? Is it too expensive? Why aren't they here now if they are reputable, credible manufacturers in other places in the world?

Dr. CRAWFORD. As I mentioned, there are only like six major manufacturers. There is only one company that manufactures influenza vaccine in the United States and that is in a Pennsylvania plant. The company that ran into difficulty is an American-owned company, but the facility is in England.

The CHAIRMAN. But you said in your opening statement, "We are encouraging foreign producers."

Dr. CRAWFORD. We are, and we are telling——

The CHAIRMAN. What in that encouragement is an impediment to them that they wouldn't come rushing to this market?

Dr. CRAWFORD. It is, as I understand it, a business decision. If your plant is in Germany, which the GlaxoSmithKline plant is, obviously, if you can get rid or sell most of your production run in Germany or close by, then you are probably going to do that. If you need the American market in order to make ends meet or to expand, then you might consider the U.S. market.

The CHAIRMAN. Does FDA accept the German licensure process?

Dr. CRAWFORD. We do not accept it exactly. We have——

The CHAIRMAN. How long is theirs and how long is yours?

Dr. CRAWFORD. Well, it is about the same. It doesn't take very long to get through that. They just have to indicate an interest in coming to the U.S. market, and we can't force them to do that under our law.

The CHAIRMAN. No, I appreciate that. I just wondered if there are obstacles out there beyond a pure business decision, costs and problems and complications involved that would suggest to them that this was a market not to come to.

Dr. CRAWFORD. There have been a number of things that have been mentioned during this crisis. One is liability concerns in the United States. There are liability concerns in all countries, but that has been something that is mentioned. I am not qualified in that area to say whether that is right or wrong. I think it probably is a factor.

Another thing that has been mentioned is FDA is very serious about regulation, as are most Western countries, and maybe the way we do the regulation is an impediment, and that is why we are examining these Good Manufacturing Practice regulations. We want to modernize them in such a way that we get the same protection perhaps quicker with less burden on the industry. I men-

tioned that is a process that is ongoing. So we are refining what we do as best we can in order to make the market more attractive. I think that could also be a factor, although I don't think it is much different than it is in any other Western country.

Then the third thing would be basically the profitability of the industry, which has been mentioned. The FluMist vaccine, for example, took a lot of doing to develop. There was a cost of development and it was greeted with a lot of enthusiasm. But the cost per dose if you buy it at the maximum discounted rate based on the volume of your purchase, I believe is lower than $20 per dose. If you compare that to a prescription for a new drug that is under patent, you know, perhaps a company—most of these companies also manufacture pharmaceuticals—it makes sense to me, although, again, I am not an expert in that area, that you can make more profitability out of a pharmaceutical than you could a vaccine.

The CHAIRMAN. You mentioned your Clear Pathways. Are there any performance measures that point to the success of your Pathways initiative? I want to ask a couple of questions on that.

Dr. CRAWFORD. Yes. The critical path that we are—process that we are under now is essentially a way that FDA can reform all of the regulatory programs it has in place, from foods to vaccine to drugs and so forth, and do it on a continuing basis. It is basically the first kind of scientific self-improvement for a regulatory agency in the world and so I think it does represent the new FDA.

I point out that we have just started with the rudiments of it in 2002 and the first successes happened in the drug area this particular year. So it is not very far along and it is not reaping the benefits that I feel confident that it will in the years to come.

The CHAIRMAN. What are the challenges that you have already identified in this approach and what do manufacturers tell you their challenges are? Can you spread for us the timeline of this kind of an initiative?

Dr. CRAWFORD. Are you talking about just vaccines or all things?

The CHAIRMAN. Well, let us focus on vaccines today. I mean, that——

Dr. CRAWFORD. Well, with vaccines, I think the industry is well aware that we are reforming these regulations and we will be asking for public input. That primarily means the academic, scientific, and industrial communities. We will be taking those commentaries next year in a way to try to fashion something that is both medically sound, adequately protects the public health, and also represents the special needs and interests of the industry. I think by engaging in this along the critical path approach, we will attract interest from the vaccine community and those pharmaceutical companies that formerly produced biologicals, as we call them, might be hopefully attracted to cranking those areas of their portfolio up again.

We are going to engage them as carefully and as well as we can, but I have to tell you that that industry has contracted over time and it is—I don't think anyone is particularly optimistic about it returning to the number of suppliers that we had before unless something unforeseen happens.

The CHAIRMAN. Well, I think we have recognized that. Both Senator Bayh and I recognized that. That is why we want to build ini-

tiative or incentives into the system, because I think I agree with you. Streamlining the process and doing all of that and trying to more clearly identify the market is one thing. Being able to provide some level of protection for those companies who invest in the market from a financial standpoint or incentive is another thing. Of course, last, to make the process a thorough, responsible one, as you will do, but to not make it so cumbering that it costs tens of millions of dollars more than it might somewhere else. That in itself is a disincentive and I hope that this Pathways process that you are about, or that you are under, will do so. By the way, the $100 million is in the budget.

Dr. CRAWFORD. Thank you, sir, very much.

The CHAIRMAN. So you are going to get that kind of money. Next year, we expect large volumes of vaccine produced by the cell process, OK?

Dr. CRAWFORD. Thank you, sir. [Laughter.]

The CHAIRMAN. All right. We expect that kind of return.

Dr. Cohen, we have been lucky that, so far, we have had what appears to be a mild flu season at the very early stages of it. Historically, does a mild start mean a generally mild season?

Dr. COHEN. Influenza, unfortunately, is one of the most unpredictable diseases. Last year, we had an early flu season and it ended early, as well. This year, we could have a mild season or it could be severe. The onset of it doesn't predict the severity or the amount of disease.

So far, worldwide, the virologic tests that have been done have shown a very low level of flu activity. Of the over 6,000 specimens that have been submitted to the surveillance laboratories, less than one percent actually have flu virus isolated from them. The good news there is that all of the isolates appear to be the isolates that are present in this year's vaccine. They are related very closely to the Fujian strain of Influenza A.

So we are keeping our fingers crossed, but it is very unpredictable and we always have to look at this very, very closely.

The CHAIRMAN. In the discussion you had with Senator Kohl about the volume of vaccines that will be available versus what is an average of usage, what happens if a worst case scenario develops? What is your plan at this moment if we get into a tremendously bad flu season and we are simply well beyond—assuming that we have had reasonable distribution to the most vulnerable of our society of the 60 million doses and we get to a very substantial situation? What do we do? What is your plan?

Dr. COHEN. Well, there are several things that we have done in preparation. One is that we have developed guidelines for the use of antiviral drugs, and, in fact, we have stockpiled enough antiviral drugs. There is enough Rimantadine, for example, to treat five million people. This would be used in a focused way, hopefully to control outbreaks that might occur in institutional settings, such as in nursing homes. So we have those efforts.

There are antiviral drugs that are available in the pipeline that can be described by practitioners, as well. These can be used to prevent disease and they also can be used to treat disease. If they are used within the first 24 to 48 hours, they can shorten the illness. So that is one approach.

The other approach is some of the things that our mothers taught us growing up that prevents disease transmission. So we have been pursuing a number of educational campaigns, trying to encourage people to do things that would interrupt transmission of disease. For example, cough hygiene, for example—if you cough or sneeze, to cover your cough; to wash your hands before you eat, after you sneeze; all of those things that would prevent you from becoming ill—keeping your fingers out of your nose, your mouth, your eyes, those kinds of things. Then particularly in times like this, if you have a sick child or you yourself are sick, you don't want to send your child to school to spread disease or you don't want to go to work to spread disease.

So there is a variety of specific things that we can do to try to prevent or make people better more quickly, and there are things that people can do to protect themselves and others.

The CHAIRMAN. Is that process or public awareness campaign underway? Is there now a timeline of implementation of it? Obviously, the antivirals are important, but I agree with you. What do we do? I think that question will get asked and you should be able to respond before it is asked in the circumstance we are now in. To be able to not meet the demand is one thing. We now know that is at hand and we hope for a very limited season. But there ought to be a very large public effort out there with our public health officials to make sure that the rest of the story is told.

Dr. COHEN. One of the other areas, we often see transmission of influenza in institutional settings and long-term care, obviously where we have many of the elderly or disabled people who are very vulnerable. We are providing guidance, as well, to those kinds of institutions. We are working closely with their trade associations, trying to tell them the things that they can do to try to prevent transmission of the disease. Again, a lot of these relate to hygiene and sanitation, the use of antivirals, the rapid use of diagnostic tests to say, "Yes, we really do have influenza and we need to implement things to try to stop it."

The educational campaigns have been ongoing. There have been various activities. For example, we have provided much information on our website. During the early part of this episode, there were over 300,000 visits a day to the website. We have been putting out public information, video and audio information, and there will be a series of print information that initially was encouraging people about the appropriate use of vaccines and foregoing vaccines if they were not high-risk, but will then change into the things that people can do to protect themselves and protect others from transmitting disease.

The CHAIRMAN. My last question of both of you before I turn to my colleague who has joined us, in your views, what is the top priority that Congress should be working on to address the issue of the vaccine shortage. Dr. Crawford.

Dr. CRAWFORD. Well, I think this research funding and also following through on what we are doing with it, because remember that the idea is that this is not basic research, this is applied research that we want to do to try to get a system together using experts in other countries from around the world so that we can produce this vaccine without going through this laborious egg proc-

ess which is going to continue to get us into trouble. I believe that if we get this done so that the cell culture type of way of producing the vaccine can be mass produced and we can get enough vaccine to get the job done, I believe it stands to be more profitable. I think it might energize the industry. I think it is the kind of thing we in the government are going to have to do for them in order to get it going.

So I would say that is the long-range thing. These things like incentives and these things like FDA improving its regulatory process are not necessarily going to result in the kind of explosion of interest that you and I would like to see because it doesn't really give them the technology to do what we are going to ask of them——

The CHAIRMAN. But it won't hurt.

Dr. CRAWFORD. It won't hurt.

The CHAIRMAN. All right.

Dr. CRAWFORD. It absolutely will not hurt.

The CHAIRMAN. Therefore, I don't want you to back away from what you are doing.

Dr. CRAWFORD. No, sir, I won't.

The CHAIRMAN. I came to this city 24 years ago, and at that time, one of the first things I heard was that the cost of health care today, or the cost of new medicines today on the market was a very laborious process that FDA puts everybody through. Now, it has ensured over time, without question, historically safe medicines. There is no doubt about that in anybody's mind. But the question remains, is there a better, cleaner, less expensive, more time sensitive way of getting this job done——

Dr. CRAWFORD. Absolutely.

The CHAIRMAN [continuing]. Still making it safe for the American public, and that is your challenge and I trust you can—you will work toward that. We will have you back next year to see how the pathway is working.

Dr. CRAWFORD. We hope to work with you and the committee on that.

The CHAIRMAN. Certainly. Thank you.

Dr. Cohen.

Dr. COHEN. Senator, I am not sure there is one answer. When I look ahead, I see that what we need is we need more vaccine. We need more domestic production of vaccine. We need to convince people that these vaccines are important in protecting their health, so we need greater demand. So there are a number of things that we potentially can do, and I think we have to work together to look at what kind of a package to put together that gets us there, to where we have more vaccines and more people who want the vaccines so there is greater demand, there is a greater economic benefit for companies to want to enter into a domestic vaccine production.

The CHAIRMAN. I am always amazed by the fact that in the generation I grew up in, my mother never questioned the importance of my childhood vaccinations. They simply got done, and we largely eliminated a variety of crippling and death-causing illnesses around this country as a result of that.

Today, that number and that desire and the demand on the part of new parents is amazing to me, the drop and decline in the understanding, the sensibility of it, and that is an educational process that I think we were much more engaged in as a country 40 or 50 or 60 years ago than we probably are today. We have simply got to get back to doing that. It does improve public health. Thank you.

Senator Carper, welcome.

Senator CARPER. Mr. Chairman, thanks very much to our witnesses. I am conducting an orientation for new Senators this week and I am helping to cohost and co-lead and I need to return to join. Our session is just about to conclude, and I apologize. I had a couple of questions I wanted to ask. I would like to maybe be able to ask them for the record, if I could, to submit them in writing?

The CHAIRMAN. Sure. Fine.

Senator CARPER. I would appreciate your following up on those. Thanks very much.

The CHAIRMAN. Thank you very much. Gentlemen, thank you.

Let us move to our second and last panel. Gentlemen, thank you for being here and we thank you for your patience. Let me introduce this panel to the committee.

Dr. Peter Paradiso, Vice President for New Business and Scientific Affairs, Wyeth Pharmaceuticals, we welcome you. Dr. Frank Sloan, Center for Health Policy, Law, and Management, Terry Sanford Institute of Public Policy at Duke University, we thank you for being here.

Dr. Paradiso, please proceed.

STATEMENT OF PETER R. PARADISO, VICE PRESIDENT, NEW BUSINESS AND SCIENTIFIC AFFAIRS, WYETH PHARMACEUTICALS, COLLEGEVILLE, PA

Mr. PARADISO. Good afternoon, Mr. Chairman and members of the committee. My name is Peter Paradiso and I am vice president for New Business and Scientific Affairs at Wyeth.

Wyeth has been in the business of researching and manufacturing vaccines and biologicals for more than 100 years and I have been part of that effort for the last 20 years. We are proud of the contributions of our products to the public health.

As important as these products are to society, the vaccine enterprise has become increasingly difficult. The shortage of flu vaccine is but a symptom of a larger problem. To address flu vaccine supply and the limited number of manufacturers, you need to understand the reasons there are so few manufacturers of vaccines of any type.

Some of the unattractive facets of the vaccine business are not inherent but are the result of government policies, some justifiable and others more questionable, that have had an impact on the development and the subsequent supply of vaccines. These barriers can hinder existing vaccine companies and act as disincentives for new participants. These derive in part from a mindset intolerant of even theoretical risk, and therefore often skew the risk-benefit ratio to the point where the benefit is forgotten.

One of the biggest changes that has occurred in the vaccine industry in the time that I have been working in this field is the changing regulatory and compliance environment. In our company,

almost all of the new hires in vaccine research over the last several years are involved in FDA compliance-related issues. Manufacturers——

The CHAIRMAN. Doctor, would you pull that mike down a little bit and maybe a little closer to you? I am 59 years old. Something is happening. Thank you. [Laughter.]

Mr. PARADISO. Manufacturing facilities that are licensed for new products are outdated within 2 years and require significant and seemingly continuous large investments.

Using our new Prevnar vaccine as an example, this product is manufactured in two facilities that were licensed in 2000. More than $300 million of capital has been invested in the existing Prevnar facilities in the last 3 years. In the same period, operating expenses have nearly doubled due largely to the need to update facilities and systems to meet evolving standards of FDA's Good Manufacturing Practices.

Due to the diligence of the FDA and the efforts of manufacturers, the safety record of vaccines' manufacturing and supply is exemplary, so it is hard sometimes to understand why we need to have still higher standards.

In the case of Wyeth's inactivated influenza vaccine FluShield, continued investment was not sustainable. The fact is that our influenza vaccine business had lost money in four of its previous five years and significantly more investment in manufacturing was required. We had eight million unsold doses of vaccine at the end of 2002 when we exited the business. We announced that we would exit the injectable fluid business and focus our resources on the new intranasal vaccine FluMist that we were developing in collaboration with the MedImmune Company. FluMist was licensed in 2003, but unfortunately, not for any of the high-risk groups for whom flu vaccine is recommended. As a result, millions of doses of FluMist went unused in 2003, even in the face of a severe early epidemic and vaccine shortages.

While Wyeth no longer makes an influenza vaccine, we are still in the vaccine business and I would now like to address some of the marketplace challenges in pediatric vaccines.

Roughly 60 percent of the U.S. market is one customer, the Federal Government. This customer has the legal power to control prices. The government-fixed price for tetanus is so low that no company has bid to provide the vaccine to the government for many years. While it is an obligation of the government to be a prudent purchaser, it is also an obligation of government to protect the public health. By overemphasizing the former, one risks jeopardizing the latter.

Another poorly understood risk for the vaccine business is liability. Vaccines are given to virtually every young child in this country and many diseases and afflictions manifest themselves in young children. The likelihood that any of these conditions would occur in temporal proximity to immunization is high just because of the frequency with which immunizations are given. Vaccines have been accused of causing epilepsy, multiple sclerosis, attention deficit disorder, cancer, auto-immune disease, learning disability, Gulf War syndrome, and even the AIDS epidemic. Today's allegations linking

vaccine to autism are but the latest in a long history of accusations, none of which have been proven to have scientific validity.

In 1986, Congress created the Vaccine Injury Compensation Program administered by the Department of Health and Human Services. Although that statute has been helpful, it needs to be reformed to reflect today's realities.

There is a widespread perception that this program completely shields companies from liability, but that is not the case. Today, companies that produce childhood vaccines have been served with over 350 lawsuits, some of them massive class actions. These suits allege that vaccines cause autism. In May 2004, the Institute of Medicine issued a report concluding that there is sufficient evidence, scientific evidence, to reject a causal relationship between autism and vaccines. Despite this, we estimate that the companies involved in this litigation have spent more than $200 million collectively in outside legal costs and the first case has not yet gone to trial.

These and other issues confront companies as they decide whether to enter or remain in the vaccine business. There are constructive steps that Congress can take.

For example, Senators Bingaman and Smith have introduced a bill that would remove the price caps on children's vaccines and allow CDC to develop a stockpile of pediatric vaccines to utilize in the event of shortages. Senators Craig and Bayh have introduced a bill that would provide tax incentives for upgrading or building a new vaccine facility and also offers a method of purchasing unsold doses of flu vaccine at the end of the year. These would be positive steps.

The FDA, as we heard, has announced a project which they call GMPs for the 21st Century. I would urge the FDA to make review of vaccine CGMPs the top priority.

Finally, the liability burden facing companies needs to be addressed. Senators Frist and Gregg made an attempt to do so last year and a new start needs to be made in the next Congress.

I am very excited about the scientific possibilities for the future of vaccines, but recent events serve as a reminder of the fragility of this enterprise.

Thank you for your attention and for this opportunity to appear before the committee.

The CHAIRMAN. Doctor, thank you.

[The prepared statement of Mr. Paradiso follows:]

Senate Special Committee on Aging Hearing

"Liability, Licensing and the Flu Vaccine Market: Making Decisions Today to Prevent a Crisis Tomorrow"

November 16, 2004

Testimony of:

Peter R. Paradiso, Ph.D.
VP, Scientific Affairs
Wyeth Pharmaceuticals

Testimony of Peter R. Paradiso: Senate Special Committee on Aging: November 16, 2004

Introduction

Good Afternoon Mr. Chairman and members of the committee. My name is Peter Paradiso and I am the Vice President for New Business and Scientific Affairs at Wyeth. Wyeth has been in the business of researching and manufacturing vaccines and biological products for over 100 years and I have been part of that effort for the past 20 years. We are proud of the contributions we have made to public health throughout this time including our contribution to the eradication of smallpox worldwide not only through the supply of vaccine but also the technology for a bifurcated needle delivery device critical to the mass immunization programs. For nearly 20 years we were also the sole U.S. producer of oral polio vaccine, which conquered polio disease in the U.S. with the last case of indigenous disease occurring in 1979.

Most recently we introduced the first conjugate vaccine to prevent meningitis and other invasive infections of childhood caused by the pneumococcal bacteria, an organism that not only causes serious diseases, but also was developing antibiotic resistance at an alarming rate. In the 4 years that this vaccine, named Prevnar, has been on the market in the U.S., childhood pneumococcal disease has declined by over 80 percent. Furthermore, studies have shown that invasive disease caused by pneumococcus in adults has also decreased significantly due to fewer ill children spreading disease to adults. In total this means that not only have serious diseases and death declined but the need to use antibiotics has decreased as well which should serve to stem the rising tide of antibiotic resistance. While I speak of Wyeth vaccines in particular, vaccines made by our competitors can boast of the same type of dramatic results in decreasing or in some cases eliminating the former scourges of childhood diseases. The record shows that vaccines have had one of, if not the greatest impact of any public health intervention over the last century.

As important as these products are to society, it has become increasingly difficult to justify remaining in the vaccine business. While the primary focus of this hearing is on influenza vaccine, the shortage of flu vaccine and flu vaccine manufacturers is but a symptom of a larger problem. There are only four companies left that make vaccines routinely used in childhood. Many vaccines are now made by only one company. And while it did not grab the public's attention to the extent of the flu vaccine shortage, during the early part

of this decade most children's vaccines experienced dramatic shortages as well. To address flu vaccine supply and the limited number of manufacturers, one must look at the small number of manufacturers overall, and understand the reasons that the current situation exists.

In February 2002, the National Vaccine Advisory Committee (NVAC), under the auspices of the National Vaccine Program Office (NVPO), reviewed the issues associated with the shortages in vaccine supplies. The conclusions of this detailed assessment highlighted numerous efforts that could impact vaccine supply in a positive way. These strategies included, among others, expansion of vaccine stockpiles, increased support for regulatory agencies, maintenance and strengthening of liability protections, financial incentives to manufacturers, streamlining the regulatory process without compromising safety or efficacy, and a campaign to emphasize the benefits of vaccination. I will highlight several of these issues in my comments but all of them are important and thoughtful approaches to the vaccine supply issue.

Every company must weigh the benefits versus the risks in each business opportunity when deciding where to place its resources. Some unappealing factors are inherent to vaccines and not to other types of drugs. As an example, most vaccines are used by children in a particular age group and for a defined and limited number of doses. This is in contrast, for example, to drugs for hypertension, which are taken by a significant portion of adults across multiple birth cohorts and are taken multiple times a day perhaps for the lifespan of the individual. Also as a society we are generally willing to pay more for products that treat diseases than for products that prevent them. One very telling figure that illustrates these points is that the total worldwide market for vaccines made by all manufacturers around the globe is estimated to be around $8 billion. There are single drugs on the market that rival the size of the global vaccine market.

Another inherent feature is that many drug products that are successful in the market find themselves with an ever-expanding market as new medical applications are found. With vaccines, the more effective a product is, the more likely it is to become obsolete. The smallpox and oral polio vaccines are both examples of highly effective products that worked themselves out of a market by eliminating disease.

I will address issues that relate to the changing environment in the vaccine field. These include changes in research and development, manufacturing, regulation,

liability and the overall marketplace dynamics. In addition, I will touch on some potential areas where this Congress can have a positive impact on securing vaccine supply.

Vaccine Research and Development

Some of the unattractive facets of the vaccine business are not inherent but are the result of government policies, some justifiable and others more questionable, that have an impact on the development process and can result in barriers that hinder existing vaccine research companies and serve as disincentives to new participants. These derive, in part, from a mindset intolerant of even theoretical risk and therefore often skew the risk/benefit ratio to the point where the benefit is forgotten. This mindset persists despite the fact that the vigilance of FDA and the efforts of manufacturers have produced an exemplary safety record.

Clinical trials for vaccines are much larger in scope than for drugs, which one would expect since these are products that are given to largely healthy individuals. The clinical trials for our Prevnar vaccine included over 40,000 children. Press reports about a vaccine to prevent childhood diarrhea under development at other companies have indicated that more than 60,000 children are in each trial. By contrast, drug trials typically involve 3000-5000 people. Importantly, however, vaccine development has become much more complex and costly over the last ten years. This ranges from increasingly stringent requirements for producing test vaccines to be used in clinical trials, to larger and more complex clinical programs. In fact, over the last five years in our company, the majority of the new hires in vaccines R&D are working in compliance, quality assurance or regulatory affairs rather than doing actual vaccine research. This has significantly increased our costs and lengthened our timelines.

Manufacturing

The complexity of manufacturing a vaccine is much higher than for small molecule drugs (e.g., pills) in part because of the use of living organisms as opposed to a more predictable chemical process and in part because of the subsequent complexity of the quality control and compliance processes. It takes approximately five years to build and validate a vaccines manufacturing

facility. As a result, it is necessary to commit to building facilities at the same time that pivotal clinical trials are starting and while their outcome is uncertain.

However, the investments in manufacturing do not end with licensure. Using Prevnar as an example, this product is manufactured in two facilities that were licensed in 2000 after inspections by reviewers from the Centers for Biologics Evaluation and Review (CBER). Since then, to improve compliance and increase production capacity, we have made significant changes in these facilities and in our manufacturing and quality processes. Over $300M of capital has been invested in existing Prevnar facilities since 2000 and operating expenses have nearly doubled in the past three years. Over 2,000 people are involved in the manufacture of Prevnar and an additional 500 people are employed to insure that we are compliant with all of the regulatory requirements. It takes, on average, 50 weeks to produce and release a batch of product. It is, in part, this timeline that makes rapid response to shortages very difficult.

Once licensed, it is possible to rationalize this level of investment for a new product like Prevnar for which we are the sole global supplier. It is much more difficult to justify the ongoing investment for older products with prices reflective of the environment decades ago. This need to make significant investments in facilities to meet ever more stringent cGMP (good manufacturing practices) requirements becomes a critical factor in deciding whether to continue to keep a product on the market. In the case of Wyeth's DTaP and influenza vaccines, this continued investment could not be justified.

The Vaccine Marketplace

Once on the market, pediatric vaccines, which constitute the bulk of vaccine products, must deal with the fact that roughly 60 percent of the U.S. market is one customer, the federal government. Having one customer with that degree of dominance in the market is daunting enough but when that customer has the legal power behind it to control prices, the market becomes much less attractive. Further, some states have ignored definitions in federal law and have taken steps that would make the percentage of the government market even greater. To date the Department of Health & Human Services (HHS) has not undertaken any activity to uphold federal law and inhibit that expansion.

When the Vaccines for Children program passed the Congress as part of OBRA '93, it created price controls on the vaccines that were on the market at that time. This situation has become so egregious that the price for tetanus vaccine is so low that no company has bid to provide it to the government for many years. Merck's MMR vaccine is listed on the government schedule at around $16.25 while the market catalog price is $38.05. Haemophilus influenzae type b vaccines are capped at $7.65/dose but are over $21.78/dose in the private market. The CDC is the largest purchaser among the government agencies, and has the leverage of a price controlled federal supply schedule, designed primarily for use by the VA and DOD, to use in driving prices downward. While it is an obligation of government to be a prudent purchaser, it is also an obligation of government to protect the public health. By over-emphasizing the former, one risks jeopardizing the latter.

Liability

One poorly understood risk of being in the vaccine business is liability. Since vaccines are so stringently regulated, both before and after marketing, and have such an outstanding record of safety, it might seem baffling why liability should be so problematic. The root of the problem lies in the fact that vaccines are given to virtually every young child in this country and as every parent knows, many diseases and afflictions manifest themselves in young children. The likelihood that any of these conditions would occur in temporal proximity to an immunization is high just because of the frequency with which shots are given.

Further, since nearly every child receives vaccines, any affliction without a known cause could be blamed on immunizations the child has received. Since the advent of the Internet, numerous unsubstantiated theories about vaccines have abounded. Over the course of the past 15 years, vaccines have been accused of causing epilepsy, multiple sclerosis, autism, attention deficit disorder, cancer, autoimmune disorders, learning disabilities, and Gulf War Syndrome. Vaccines have even been accused of being the cause of the AIDS epidemic. Today's allegations linking vaccines to autism are but the latest in a long history of accusations, none of which have been proven to have scientific validity.

While there were many more manufacturers making children's vaccines in the 1970's, that number has dwindled now to just four. The decrease has several causes but clearly the mostly precipitous decline occurred in the early 1980's as

manufacturers left the market due to an explosion of lawsuits alleging damage from DTP vaccine. This explosion of litigation scared liability insurers away from vaccines and companies were left with no insurance coverage. The situation became so perilous that there was only one company left making this vaccine, which prevents diphtheria, tetanus, and whooping cough, and public health officials had to take the step of not immunizing two year olds against these diseases because of vaccine shortages. The one remaining company was forced to raise its price to cover the cost of litigation and at the height of the problem fully 75 percent of the cost of DTP vaccine was directly attributable to the cost of litigation.

Congress intervened in 1986 and created the Vaccine Injury Compensation Program (VICP) administered by the Department of Health & Human Services to cover vaccines routinely recommended for use in children. This program was created to ease recovery for alleged vaccine-related injuries while protecting manufacturers from the costs and uncertainties of litigation that could potentially jeopardize the Nation's vaccine supply. There is a widespread perception that this program shields companies from liability but that is not the case. The law requires that anyone alleging an injury from a vaccine must first file a claim in the compensation program. However, whatever the decision from the program as to whether or not the injury was actually caused by a vaccine, the claimant has a right to leave the compensation program and proceed against the vaccine manufacturer in civil court. Furthermore, if a claim has been pending for more than 240 days and no decision has yet been rendered, a claimant can opt out of the program and proceed against the vaccine manufacturer in civil court.

The VICP determines the validity of claims based on the preponderance of the scientific evidence. A petitioner who has sustained an injury on the table of compensable events during the specified time period is presumed to have a vaccine related injury and is compensated by the VICP without having to actually demonstrate causation or fault. If a petitioner brings a claim for an injury that is not listed on the table, then the petitioner must show by the preponderance of the scientific evidence that the injury was caused by vaccine, but unlike civil court, the claimant does not have to demonstrate that the vaccine was defective. Since the inception of the program in 1986, the Institute of Medicine has done periodic reviews of scientific studies and has reached various conclusions related to causation which have in turn aided the VICP in determining causation.

Today, companies that make children's vaccines are facing a liability situation that dwarfs that of the 1980's when manufacturers were driven from the market. Each company has been served with over 350 lawsuits, some of them massive class actions, alleging injuries arising from the vaccine preservative thimerosal. There are also 4200 related pending petitions in the VICP, which are proceeding together as part of the Omnibus Autism Proceeding. These petitions, which may one day turn into lawsuits directed at manufacturers, allege that autism may be caused by MMR vaccination or the preservative thimerosal, formerly found in other childhood vaccines, or by some combination of the two.

In May 2004, the Institute of Medicine issued a report concluding that there is sufficient scientific evidence to reject a causal relationship between autism and vaccines. Although to date, not one of the 350 or so lawsuits has proceeded to trial, we estimate that the companies involved in this litigation have spent more than $200 million collectively in outside legal costs. Actual trials seeking damages for injuries are scheduled to commence early next year, at which point the legal costs will increase exponentially. Further, executives and scientists from the companies will spend countless hours in depositions and at trial. While there is overwhelming scientific evidence refuting any alleged link between vaccines and autism, no company would want the dynamics of a jury contemplating a disabled child versus a faceless corporation.

Recent Changes in the Wyeth Vaccine Business

All of the factors laid out above serve as the context in which our decision was made to leave various vaccine businesses including flu vaccine, and the routinely used DTaP vaccine for children. Regarding influenza, Wyeth had produced this vaccine in Marietta, PA, for nearly 20 years. A new manufacturing facility was built in the 1990s and licensed in 1998. We announced in November 2002 that the 2002-2003 would be our last season in the business. Our influenza vaccine business had lost money in four of its previous five years due largely to doses left unsold at the end of each season. Compounding that situation was the fact that in 2000, two years after licensure of the new manufacturing facility, the FDA informed us that extensive changes would need to be made at the site to remain in compliance with evolving standards. Wyeth reached an agreement with the FDA to enter into a consent decree focusing on the company's compliance with current Good Manufacturing Practices (cGMP). One of the sites involved was our flu manufacturing facility in Marietta, PA. When this significant compliance action was taken, FDA publicly acknowledged that there had been no safety

risk to patients with any products that had been made at that site. During the interval from 2000 to when we close the doors at the facility at the end of this year, we will have invested over $100 million in capital improvements for that facility alone. We could not justify further investment. If we had opted to persist in the flu vaccine business, many more millions of dollars in investment would have been required and our manufacturing costs would have continued to escalate.

Faced with this financial prospect and coupled with the fact that we had eight million unsold doses of vaccine at the end of 2002, which signaled that ample supply of vaccine was available from two other manufacturers, the only rational decision was to leave this flu vaccine business.

Our decision to leave the DTaP business had some common factors with the flu situation. The facility in Pearl River, NY where DTaP was produced was also subject to the consent decree we agreed to in 2000. We had known for several years that our DTaP had a limited lifespan in the market. Pediatricians and public health officials were understandably interested in combining some of the children's vaccines into one shot to reduce the number of injections given to babies. We had undertaken clinical trials to combine our Hemophilus influenzae type b (Hib) vaccine with DTaP, but our trials showed, as did the trials of other manufacturers, that combining these products resulted in a diminished immune response to the Hib component. Other potential vaccines that could be combined with DTaP were Hepatitis B and inactivated polio vaccines. Since we did not make either of those but our competitors did, we realized that our DTaP would not be a viable product much longer. In July 1999, the U.S. Public Health Service asked manufacturers to move away from using the thimerosal preservative in their vaccines. The U.S. Public Health Service and the American Academy of Pediatrics felt that removal of this preservative would be a means of maintaining parental confidence in vaccines while both organizations acknowledged that there was no scientific evidence to suggest any danger from the product. Our vaccine would have required a new manufacturing process, clinical trials, and re-licensure. These development requirements, coupled with the significant facility investments and the short projected lifespan of the product all contributed to our exit from this market.

Potential Solutions

These are examples of the types of decisions facing vaccine companies in terms of justifying remaining in this business relative to other investment opportunities. As mentioned, some of relatively unattractive components of the vaccine business are inherent. Others, however, can and should be addressed. Senators Bingaman and Smith have introduced a bill (S. 2272) that would remove the price caps on children's vaccines. It would also implement a technical change needed by the CDC in order to develop a stockpile of pediatric vaccines to utilize in the event of shortages. And it would transfer a category of needy children from an appropriated CDC account to an entitlement program which would not only benefit these children and the state public health departments that serve them but would also help manufacturers of new vaccines to know that government funds would be available to pay for the roughly 60% of the market controlled by the government.

Senators Craig and Bayh have introduced a bill (S. 2038) that would provide tax incentives for upgrading or building a new vaccine facility. This would help diminish the cost differential spread between drug and vaccine facilities and would be very helpful, particularly if constructed so that the tax credits could be carried forward. S. 2038 also offers a method of purchasing unsold doses of flu vaccine at the end of the season.

The FDA has announced a project, which they call "GMPs for the 21st Century." Part of this endeavor is an examination of cGMP's (current good manufacturing practices) to determine if they are the correct approach. I would urge the FDA to make review of vaccine cGMP's a priority. The safety bar on vaccines must remain high but if FDA changes the requirements for cGMP it should only do so because of some demonstrable threat to the safety of the final product, not because it is possible to conduct a process differently. And finally, the liability burden facing companies needs to be addressed. Senators Frist and Gregg made an attempt to do so last year and a new start needs to be made to ensure that manufacturers are not crippled from lawsuits born of unsubstantiated claims.

Conclusions

In closing I would like to say that as a research scientist, I am very excited about the future of vaccines. Over the past 20 years I have been privileged to

be a part of the development of a number of childhood vaccines such as HibTITER, Meningitec and Prevnar that have had a dramatic impact on the health of children here and around the world. Advances in technology allow us to contemplate vaccines today that were beyond our dreams just a decade ago. At Wyeth, for example, we are working not only on vaccines for unconquered infectious diseases but also for conditions like Alzheimer's disease. Unfortunately while the scientific frontier is very exciting, the business barriers can be daunting. This is particularly true of companies contemplating entering this marketplace anew or maintaining an aging product portfolio. Thus even though we have been in the vaccines business for many years, we have discontinued several vaccine products in the past five years and have closed a vaccine research facility in Rochester, New York and a manufacturing facility in Marietta, PA. We remain committed to continuing our work in vaccine development because we recognize the incredible public health potential of these products and we hope that recent events will serve as a reminder of the fragility of this enterprise.

So I thank the committee for giving us the opportunity today to present our views and would urge you to continue to pursue ways to improve the business environment and stabilize the vaccine industry.

The CHAIRMAN. Dr. Sloan, thank you for being with us.

STATEMENT OF FRANK A. SLOAN, CENTER FOR HEALTH POLICY, LAW, AND MANAGEMENT, TERRY SANFORD INSTITUTE OF PUBLIC POLICY, DUKE UNIVERSITY, DURHAM, NC

Mr. SLOAN. Thank you. Mr. Chairman, I appreciate the opportunity to appear before you today. I recently chaired the Institute of Medicine's Committee on the Evaluation of Vaccine Purchase Finance in the United States. The full report, "Financing Vaccines in the 21st Century: Assuring Access and Availability," was released in August 2003 and is published by the National Academies Press.

Although the report applied to childhood and adult vaccines in general, the findings and recommendations of the report have even greater force today than in late 2003 given the substantial shortage of flu vaccine the United States is currently experiencing. Although each shortage is unique, the current shortage follows a pattern of shortages for flu and other vaccines. While short-run solutions may be devised specifically for flu, the recent crisis represents an important wake-up call and presents an opportunity for consideration of longer-run and more comprehensive reforms.

The charge to the IOM committee was, (1), examine current arrangements for purchasing and distributing vaccines. (2), identify strategies to ensure access to vaccines and offer incentives for the development of new vaccines. (3), develop recommendations to guide public decisionmaking.

The committee was hampered by lack of data, including data on vaccine manufacturing and R&D costs and on liability costs. We heard that these were issues, but never could get quantitative estimates.

The national immunization system has made important progress, as our report documents. Yet despite many successes, many problems remain. Structural and financial problems plague the vaccine supply system, which are not unique to flu vaccine. For example, recent unprecedented shortages in 8 of the 11 routine childhood vaccinations caused serious delays in immunization.

The committee was concerned about the degree of concentration of firms that produce vaccines for the U.S. market. From 1966 to 1977, half of all commercial vaccine manufacturers stopped producing vaccines and this exodus has continued. Today, only five companies produce all vaccines recommended for routine use by children and adults, and only three of these are U.S.-based firms. Eight critically important vaccines have only one supplier. A long-term shut-down in capacity of any of these companies could be devastating. Experts suggest it could take years to replace vaccine license and available to the public in sufficient quantities.

The current situation with flu vaccine brought about by a dearth of suppliers is a harbinger of shortages to come. There are also delivery problems in vaccines to the public, particularly for childhood vaccines. Also, many adults, an indeterminate number, do not have insurance coverage for recommended vaccines.

A strong relationship exists between the system for purchasing and providing vaccines to the public on the one hand and stability and growth of the United States supply system on the other. The thrust of public policy for childhood vaccines has been to con-

centrate purchasing power in the Federal Government. The government uses its purchasing clout to negotiate substantial discounts and enforce price caps. Further growth of the government market share, in fact, seems as likely to create disincentives for private vaccine companies to develop new vaccines and to provide vaccines on a continuous and as-needed basis. Lack of adequate financial incentives are responsible for the vulnerability to shortage we are currently experiencing.

The committee considered several strategies ranging from incremental changes in the current system to comprehensive changes. Each alternative, and there were seven in total, has pluses and minuses and each is worth considering. But in the end, the committee recommended one of these seven alternatives.

The approach ultimately selected was a unified approach to vaccine finance and is contained in the committee's three recommendations. The first proposes a substantial redesign of the system for purchasing and financing vaccines. The recommendations state the current system for purchasing and distributing vaccines should be replaced by a vaccine mandate subsidy and voucher system. The mandate would require that all public and private insurance plans cover immunizations that, (1) yield benefits in excess of cost, and (2) only for those groups for which benefits exceed costs, and (3) for immunizations with substantial spillovers or externalities, both health and financial.

The mandate addresses several concerns, the major one being that many vaccines not only benefit the person being vaccinated, but others, even strangers, as well. The mandate would apply to all private insurers, both State regulated and self-insured employer plans, and to all public insurance plans. The subsidy provision means the Federal Government assumes responsibility for paying for the vaccines that are mandated, at least in part. Health plans will receive payments from the Federal Government for vaccine purchase and administrative fees.

While the funded mandate would cover everyone who is insured, the voucher provision would cover everyone who is uninsured. Under this plan, uninsured children and adults would receive immunizations from the health care providers of their choice and the government would reimburse providers for each vaccine plus an administration fee.

The committee proposed that a subsidy amount be determined for vaccines not yet available as a way to stimulate their development and licensure. The amount of subsidy would be based on the total societal benefit of the vaccine, not 100 percent of value, but some percentage of that amount that at a minimum reflects the health and financial benefits accruing to others than the person being vaccinated.

The expectation is that, on average, this approach will increase the prices of vaccines. While this may be a tough sell in today's fiscal environment, it is important to place this spending in context. The entire global market for all vaccines is about the same as one of several blockbuster drugs.

The subsidy should be based on an objective benchmark, the actual savings to society resulting from the discovery and use of the vaccine. The subsidy should be set by an independent body by a

completely transparent process and a methodology consistent across all vaccines. In my opinion, this should not be a fixed government price, however is a fixed dollar subsidy reflecting social benefit rather than either production or R&D costs.

The committee also recommended changes in the composition of decisionmaking process of the Advisory Committee on Immunization Practices, and as a third recommendation, called for a public process of stakeholder deliberations to explore the full implications of the proposal and address technical design issues. There have been some public meetings since the release of the report, but to my knowledge, there has been no refinement of either the IOM Committee's recommendation or an in-depth exploration of the alternatives examined in the report.

Events since the release of report, in particular the experiences with flu vaccine both this year and in the previous year, point to the need for change. Hopefully, as short-run solutions for the shortage of flu vaccine are examined, the current shortage will also be seen as an occasion for consideration of longer-run reforms affecting flu as well as other vaccines.

Thank you for the opportunity to speak before the committee today.

The CHAIRMAN. Doctor, thank you very much. I will search out your report and read it and examine it.

Mr. SLOAN. Thank you.

[The prepared statement of Mr. Sloan follows:]

Prepared Statement
Frank A. Sloan, Ph.D.
Senate Special Committee on Aging Hearing:
"Liability, Licensing and the Flu Vaccine Market: Making Decisions Today to Prevent a Crisis Tomorrow"

November 16, 2004

I appreciate the opportunity to appear before you today. I recently chaired the Institute of Medicine's Committee on the Evaluation of Vaccine Purchase Finance in the United States. The full report, *Financing Vaccines in the 21st Century: Assuring Access and Availability,* was released in August 2003 and is published by the National Academies Press (2004). Although the report applied to childhood and adult vaccines in general, the findings and recommendations of the report have even greater force today than in late 2003, given the substantial shortage of flu vaccine the U.S. is currently experiencing. Although each shortage is unique, the current shortage follows a pattern of shortages for flu and other vaccines. While short-run solutions may be devised specifically for flu, the recent crisis represents an important wake-up call and presents an opportunity for consideration of longer-run and more comprehensive reforms.

The charge to the IOM committee was to: (1) examine current arrangements for purchasing and distributing vaccines; (2) identify strategies to ensure assess to vaccines and offer incentives for the development of new vaccines; and (3)

develop recommendation to guide public decision-making. The report was prepared by an 11-member committee, which included a broad range of perspectives, ranging from adult and pediatric medicine, vaccine and insurance industries, economics, and law. The committee commissioned a survey and eight independent studies covering such issues as vaccine industry and market structure and trends, vaccine pricing trends, insurance practices and coverage levels, and disparities in access to vaccines. The committee convened expert panels on the insurance and vaccine industries, and public health. More than 100 informational interviews and meetings were with stakeholders and others. The committee was hampered by lack of data, including data on vaccine manufacturing and R&D cost and on liability cost.

The national immunization system has achieved high levels of immunization for children, and progress has been made in adult immunization as well. In particular, the Vaccines for Children program instituted in 1994, has increased immunization rates for young children that are at historic highs.

Yet despite many successes, many problems remain. Structural and financial problems also plague the vaccine supply system, which are not unique to flu vaccine. For example, recent, unprecedented shortages in 8 of the 11 routine childhood vaccines caused serious delays in immunization. The committee was concerned about the degree of concentration of firms that produce vaccines for the

U.S. market. From 1966 to 1977, half of all commercial vaccine manufacturers stopped producing vaccines, and the exodus has continued. Today only 5 companies produce all vaccines recommended for routine use by children and adults, and only three of these are U.S.–based firms.[1] Eight critically important vaccine products have only one supplier. A long–term shut–down in capacity of any one of these companies could be devastating--experts suggest that it could take years to have a replacement vaccine licensed and available to the public in sufficient quantities. The current situation with flu vaccine, brought about by a dearth of suppliers, is a harbinger of shortages to come.

There are also problems in the delivery of vaccines to the public, particularly for childhood vaccines. Similarly, many adults do not have insurance coverage for recommended vaccines.

The fragmented system for financing immunizations burdens in physicians' offices--from identifying who is eligible for immunization coverage to creating separate storage areas for vaccines for different payers. Consequently, there is a risk that physicians refer patients to public health departments, which imposes extra time and inconvenience on patients and thus is a deterrent to being immunized. The committee was concerned that, as the costs of vaccines increase,

[1] More than five manufacturers are licensed to produce vaccines, but they produce non-routine vaccines such as for anthrax.

insurers may simply drop coverage for some or all vaccines or increase cost–sharing.

A strong relationship exists between the system for purchasing and providing vaccines to the public, on one hand, and stability and growth of the U.S. vaccine supply system on the other. The thrust of public policy for childhood vaccines has been to concentrate purchasing power in the federal government. The government uses its purchasing clout to negotiate substantial discounts and enforce price caps. Further growth of the government market share in vaccines is likely to create disincentives for private vaccine companies to develop new vaccines and to provide vaccines on a continuous and an as-needed basis. Lack of adequate financial incentives are responsible for the vulnerability to shortage we are experiencing today.

The committee considered several strategies ranging from incremental changes in the current system--for example, expansion of the Vaccines for Children program to include adults--to a system of complete governmental purchase of vaccines. Each alternative has its pluses and minuses; in the end, the committee's recommendations reflect a careful balancing of the major alternatives.

The approach ultimately selected was a unified approach to vaccine finance and is contained in the committee's three recommendations. The first proposes a substantial redesign of the system for purchasing and financing vaccines. This

recommendation states that the current system for purchasing and distributing vaccines should be replaced by a vaccine *mandate, subsidy* and *voucher* system.

The *mandate* would require that all public and private insurance plans cover immunizations that (1) yield benefits in excess of cost and (2) only for those groups for which benefits exceed cost, and (3) for immunizations with substantial spillovers or externalities—both health and financial. The mandate addresses several concerns, the major one being that many vaccines not only benefit the person being vaccinated, but others (even strangers) as well. The mandate would apply to all private insurers—both state regulated and self–insured employer plans, and to all public insurance plans.

The *subsidy* provision means that the federal government assumes responsibility for paying for vaccines that are being mandated, at least in part. Health plans will receive payment from the federal government for vaccine purchase costs and administration fees.

While the funded mandate would cover everyone who insured, the *voucher* provision would cover everyone who is uninsured. Under this plan, uninsured children and adults would receive immunizations from health care providers of their choice, and the government would reimburse providers for each vaccine plus an administration fee.

The committee proposed that a subsidy amount be determined for vaccines that are not yet available as a way to stimulate their development and licensure. The amount of the subsidy would be based on the total societal benefit of the vaccine – not 100% of the value, but some percentage of that amount that, at a minimum, reflects the health and financial benefits accruing to others than the person being vaccinated. Current vaccines require more modest incentives in order to maintain investment in current capacity, promote development of better versions of old vaccines, and stimulate additional firms to enter the field. Thus, the subsidy formulas for current and future vaccines might be different.

The expectation is that, on average, this approach will increase the prices of vaccines. While this may be a tough sell in today's fiscal environment, it is important to place this spending in context—the entire global market for all vaccines is about the same as for one of several blockbuster drugs.

The subsidy should be based on an objective benchmark—the actual savings to society resulting from the discovery and use of a vaccine. The subsidy should be set by an independent body, by a completely transparent process, and the methodology must be consistent across all vaccines. This is not however, a government fixed price, but rather a fixed dollar subsidy reflecting social benefit rather than either production or R&D cost.

The committee's second recommendation proposes changes to the composition and decision making process of the Advisory Committee on Immunization Practices (ACIP)—the entity that recommends vaccines for use by the public. The group would have responsibility for reviewing evidence on benefit versus cost for existing vaccines and those not yet developed, for identifying those populations for which the net benefit is the highest, and for setting the value of the fixed dollar subsidy.

The third recommendation calls for a public process of stakeholder deliberations to explore the full implications of the proposal and address technical design issues. There have been some public meetings since the release of the report but, to my knowledge, there has been no refinement of either the IOM committee's recommendations or the alternative policies examined in our report.

Events since the release of the report, in particular the experiences with flu vaccine both this year and in the previous year point to the need for change. Hopefully, as short-run solutions for the shortage of flu vaccine are examined, the current shortage will also be seen as an occasion for consideration of longer run reforms affecting flu as well as other vaccines.

Thank you.

Testimony Before the Senate Special Committee on Aging "Liability, Licensing and the Flu Vaccine Market: Making Decisions Today to Prevent a Crisis Tomorrow"

November 16, 2004
Frank A. Sloan
J. Alexander McMahon Professor of Health Policy and Management and Professor of Economics
Duke University

Immediate Problem and Long-Run Solutions

- Recent flu vaccine shortage another "wake up" call
- Details of immediate causes of vaccine shortages differ but results are the same
- Solving flu vaccine shortages as part of a larger comprehensive solution

Charge to the Committee

(1) Examine current arrangements for purchasing and distributing vaccines in the public and private health sectors;

(2) Identify strategies that will ensure access to vaccines and offer incentives for the development of new vaccines;

(3) Develop recommendations to guide federal, state, and congressional decision-making.

Conclusion

A direct relationship exists between the financing of vaccine purchases and the stability of the U.S. vaccine supply. Financial incentives are necessary to encourage the development of new vaccines.

Conclusion

The vaccine recommendation process does not adequately incorporate consideration of a vaccine's price and societal benefits.

3 Major Recommendations

- Represent a unified approach to vaccine finance
- Designed to create incentive of entry into the vaccine industry
- Designed to encourage stable production of existing and investments in R&D on new vaccines

Recommendation 1:

Three key components

- a government mandate
- a government subsidy, and
- a government voucher for vaccines

The Mandate

- All private health insurance plans.
- All public programs (Medicaid, Medicare, SCHIP, FEHBP, state medical assistance; civilian/military employees health insurance).

The Subsidy

- The government will subsidize private and public insurers for vaccinations covered by the mandate.
- The subsidy will be based on the social benefit of the vaccine.
- The subsidy will reflect the value of vaccine and vaccine administration by health personnel.

The Voucher

- Uninsured people will receive a voucher equivalent to the subsidy to cover the costs of each vaccine.
- Providers will submit vouchers for payment by the government.

Recommendation 2:

Change ACIP membership and procedures to associate vaccine coverage decisions with social benefits and costs.

Recommendation 3:

- Stakeholder deliberations
- Evaluation plan
- Research agenda

Next Steps

- Report offers a strategic framework and blueprint for change
- Not an immediate roadmap or "next steps" plan
- Implementation requires public deliberation guided by evidence

The CHAIRMAN. Dr. Paradiso, President Bush recently signed legislation that makes some changes in the Vaccine Injury Compensation Program. Are you familiar with that?

Mr. PARADISO. Yes.

The CHAIRMAN. In this last tax bill, there was an expansion. What will this do to the current liability situation that is within the compensation fund? Will it help? We believe it would. That is why we did it. Have you evaluated it? Secondarily, you said it needs to be reevaluated again, I believe in your comments, or some adjustments made in it. Would you address those two issues?

Mr. PARADISO. Yes, I would be happy to. First of all, I have to tell you that I am not an expert on the compensation program. The issue with the compensation program, however, is that plaintiffs' attorneys have found ways to circumvent that system and as a result, cases that would normally have come before the system are now going to the courts. I mentioned in my testimony that the latest example of that is the lawsuits currently facing manufacturers relating to causes of autism. We have now 350 lawsuits, as I mentioned, that are not in the Vaccine Injury Compensation system. It is really these methods to circumvent the system that need to be taken care of.

I think some of the changes that have been made have been on the basis of adding vaccines to the system, and that is a fairly regular upgrading of the compensation system, but it hasn't addressed, I think, some of the basic issues that has led to these lawsuits.

The CHAIRMAN. Have you found the regulatory intolerance for risk that you mentioned a result of legislative confines or as a result of administrative rulemaking? Has Congress passed laws that do more harm than good, in your opinion?

Mr. PARADISO. I think the environment that I spoke of that is totally averse to theoretical risk or risk in general——

The CHAIRMAN. How about zero? That is what everybody wants nowadays, the perfect environment.

Mr. PARADISO. As a result, when you are faced with regulations that talk about current Good Manufacturing Practices, you are really not talking about a fixed set of regulations. You are actually talking about an interpretation of regulations and setting the standard for the definitions for Good Manufacturing Practices is not easy and can be expanded more or less depending on where the technology takes you and depending on how strict and how risk averse you want to be in that interpretation.

In an environment where, as you say, zero risk is tolerated, the regulatory agencies are put in a position where they are responding, to a certain extent, from what they are hearing from the public and perhaps from Congress. I think the result has been a good faith attempt to raise the standards and improve the safety of vaccine products, but I think in my experience over the last 20 years, what has happened is that those requirements have become quite onerous.

So for us, in developing a new vaccine or in keeping a vaccine on the market, what is required has taken some quantum leaps over the last at least 20 years that I have been in the business and

it just makes it harder and harder for us to stay with products and to develop new products.

The CHAIRMAN. Let me ask this question in as constructive a way as I can because it is a bit hypothetical, although it is based on the reality that both Evan Bayh and we thought we saw in the marketplace and what we have tried to do in addressing the legislation that you mentioned.

You also mentioned that you as a company have gotten out of the flu vaccine market. Walk me through, let us say, a comparative process where we would give tax credit for the constant updating that you are talking about and/or after CDC makes the projections into the market on an annual basis as to volumes necessary and, of course, you all determined the active virus involved and you begin manufacturing and the season didn't materialize. So we negotiate a compensation to move that product off the shelf and out of the market, obviously, at the end of the season. Would that have kept—this is very difficult to ask because I know you can't say, "Well, of course it would, but would it have helped a company like Wyeth stay in the market?"

Mr. PARADISO. Let me start by just addressing the flu vaccine business itself.

The CHAIRMAN. If you would, please, because that seems to be the most complicated.

Mr. PARADISO. It is, and there are things that are distinct about the flu vaccine business from other vaccines.

The CHAIRMAN. Yes.

Mr. PARADISO. The greatest distinction is that it is a seasonal vaccine business. So the vaccine changes 90 percent of the years, so there is no shelf life.

The CHAIRMAN. It is a new product.

Mr. PARADISO. So at the end of the year, you throw away what you don't use. So if there is a delay or there is an issue with vaccine supply and you can't sell the doses in January, February, and March. So that is No. 1.

Second, the paradigm, in this country has been to vaccinate in October and November. When Thanksgiving comes, vaccination stops. So in some of the years leading up to 2002, when vaccine was really not in a shortage but rather coming later in the season, vaccine was coming out in November and December. There was enough for supply but vaccination had stopped by that time and so doses were left unsold. In other years, there is 95 million doses made—that was the year 2002—and the demand was only for 80 million doses. Excuse me, 95 million doses were made and the demand was only for 80 million.

Third it is a very hard market to predict. It is very hard to predict what the season will be in terms of timing and severity. It is very hard to predict how many people are going to want to get vaccinated every year and whether vaccination is valued in any particular year.

So it really is hard to say what it is that would incentivize people to stay in the flu business. I think, obviously, any help as you suggested with tax credits or otherwise that would help defray the cost of upgrading the manufacturing process and keeping facilities in compliance would be useful.

But I think it is important that any way to ensure that the doses that we predict or that the CDC predicts are going to be required for a given year will, in fact, be utilized. If there is a safety stock, if you want to project 25 percent above that, then there needs to be some incentive for manufacturers to over-produce in a given year because the way it is now, if you are over-producing and you can't sell it by the end of November or early December, as we said, "That vaccine will not be used."

So it is not a simple problem for flu, but I think there are things that can be done, as you suggested.

The CHAIRMAN. Well, I am beginning to learn that in the time that I have spent with this issue over the last couple of months, holding the hearings later and, of course, as the whole situation developed. It is a relatively complicated process, but it does appear there are some looming problems.

As I said in my opening statement, the issue of liability, the issue of licensure and regulatory process, this constant moving to the assurity of a zero risk environment that all the world wants nowadays but never has existed and never will exist is a great problem, and so we will try to put our finger in a couple of those holes to see if we can shore up the dike a bit and I thank you for being here today.

Dr. Sloan, in one of your evaluations as to how we do traditional benefit-cost standards so we result in the Federal participation, you talked about involving—well, let me see if I can find the language here. The amount of the subsidy would be based on total societal benefit of the vaccine, not 100 percent of the value, but some percentage of that amount that, at a minimum, reflects the health and financial benefits accruing from other than the persons being vaccinated. How do you justify, then, a subsidy to somebody who is 80 years old, not in the workforce and not really contributing to the productivity of society? How do you put a social value to that one?

Mr. SLOAN. OK. When that person gets sick, very sick with the flu, the person ends up in the hospital. The person ends up going to physicians, costing the Medicare program thousands of dollars. That cost is not borne by the 80-year-old but is borne by all of us who contribute to the Medicare program. These are called financial externalities. These are substantial. So for an insured population, or even an uninsured one, because if an uninsured person ends up in the hospital, that hospital care will be covered one way or another, not by that individual, or at least a large part of it not by that individual.

So it is not only the health externalities, like in the nursing home where we talk about people making other people sick, but it is because we have assumed a social obligation. We have taken on a social obligation to care for people who get sick. That is a burden that we all share and the individual does not have the incentive.

If somebody has an income of $20,000 a year and you said, "Well, now you are at risk for a hospitalization and we are going to charge you $10,000, and then for those three or four physician visits we are going to charge you another $500, they would look at this differently than having just the front-end Medicare deductible for the hospitalization."

The CHAIRMAN. That was valuable. I knew where you were going, but I thought that was important for the record. There are a variety of ways of measuring social values in this country and we have taken them on in a variety of aspects of who the contributors are or what the costs are as it relates to, if you will, the social or the policy obligation that this country has assumed.

You commented on a fragmented system for financing, but is that causing the shortage this year?

Mr. SLOAN. Not in flu vaccine. It is causing other shortages. One of the problems that we heard as a committee was that this isn't shortage of vaccine but the shortage of vaccinations. Pediatricians in particular had patients who had various sources of financing and they couldn't figure out who in the world is covering them, whether the patient is covered. They are having to store vaccines in different bins in their refrigeration area, et cetera, and it just is a hassle to figure all of this out.

So some of them are saying, let me just refer these patients to health departments, and then a lot of people in our country don't know where a health department is or it is an inconvenience to go and so they don't get the vaccine.

The CHAIRMAN. How do we increasingly involve the government in this business and yet avoid the very thing that I heard Dr. Paradiso say, and that is in relation to the government being a large consumer and a price-fixer of product and, therefore, driving down the profitability and taking the incentive out of the marketplace?

Mr. SLOAN. Well, in my view, we don't want a price-fixer, and anything—if our program, if there was some worry that our plan would lead to price fixing, we certainly don't want to lead to price fixing.

The CHAIRMAN. In your discussions about your program, did you get to that point? Was that a part of your discussions at any point in time?

Mr. SLOAN. Certainly, the idea that the government would set the price. I mean, maybe there would be a maximum price. If we thought, for example, the flu vaccine was worth $300 a dose and a manufacturer wanted to sell the vaccine for $305 a dose, the government at some point should say, "Well, this is just way overpriced." But we would rely on competition to set the price of vaccines, so HMOs and the Medicare HMOs would negotiate the prices. So what we are talking about is a subsidy for the vaccine.

The CHAIRMAN. Am I right in asking this question, that it appears that more vaccine production is now going on overseas than it is here in the United States?

Mr. SLOAN. That is true, and we have——

The CHAIRMAN. Why is that happening?

Mr. SLOAN [continuing]. Lost a lot of vaccine——

The CHAIRMAN. Are other countries losing the same amount of contributors to the market as we, or are we driving them out?

Mr. SLOAN. I don't know whether they have—there is a lot of production—currently for flu, there is no shortage abroad and we have a shortage here, so there is clearly some supply out there. What our analysis is that in the United States, for the U.S. market, it is much more attractive for a pharmaceutical manufacturer

to make a blockbuster drug like a Lipitor which is taken every day than it is to supply vaccine on a seasonal basis to people who maybe don't realize the value of what they are getting.

One of the problems is the public isn't very educated in the value of this vaccine. Maybe they don't care completely because if they go to the hospital, they are subsidized and all that. But there is a lack of awareness of the importance of vaccines. If you look at the cost-benefit ratios, in those terms, vaccines are a very attractive investment.

The CHAIRMAN. Gentlemen, I am out of time and I apologize. There are other questions that I wanted to ask. Let me ask this closing question of both of you. Is there something that you haven't said yet that you want to say for the record on this issue? Dr. Sloan?

Mr. SLOAN. We found very little in our study about liability, but in another area that I have studied—I have looked at no-fault for neurologically impaired infants and we heard the same story in Florida and in Virginia, where the State legislature had thought that they had capped the problem by establishing a no-fault program. For the trial bar, it was much more attractive to bring a tort suit than it is to file a no-fault claim and they found ways around this, and I do think that we do need to study it.

The CHAIRMAN. More attractive meaning more profitable for them?

Mr. SLOAN. Profitable.

The CHAIRMAN. Thank you. That is what I thought you said.

Mr. SLOAN. The problem is that we don't have the good data or liability, in this one case just spoken about today we hear the figure 350 lawsuits, but we really haven't seen the whole panoply of lawsuits that are out there. I mention this because you said that the hearing has "liability" in its name.

The CHAIRMAN. Yes.

Mr. SLOAN. We also need to be looking at the incentives. We need to provide more incentives for pharmaceutical manufacturers to produce vaccine and sell vaccine in the United States.

The CHAIRMAN. Dr. Paradiso.

Mr. PARADISO. Yes. I would like to comment just that I think the overriding factor here is valuing the vaccines. We made some comments here about assigning value. We talk about vaccines in terms of cost-benefit. I think you had a comment about the cost should be equivalent to the benefit. Well, in fact, for vaccines, that is the paradigm we use, where we try to match the actual cost of the vaccine to what we are going to be saving as opposed to saying, we are going to be saving an incredible number of lives. We have to assign a value that is proportionate to that compared to everything else we do from a public health perspective. I think if we do that, then we will understand that the value of vaccines is incredible.

We have just had an experience with our Prevnar vaccine. It is a vaccine for pneumococcal disease in babies. That vaccine was introduced in the year 2000 and it has had a dramatic impact on pneumococcal invasive disease in young children, including meningitis, in the last four years, so that the disease is greatly reduced in that population.

But over and above that, and unexpectedly, it turns out that those children were spreading that disease to their parents and to their grandparents, and in the last four years, there has been a significant decline in pneumococcal invasive disease in the elderly in particular who are at high risk for pneumococcal pneumonia. In fact, those percentages are 30 or 40 percent reductions in invasive pneumococcal disease in a population that is not vaccinated.

This is a story that is happening now. It is a story that happened with polio. It is a story that happened with smallpox and measles. It is a continuous story with vaccines. So we need to understand the importance of this venture from a value perspective and treat it that way, and I think if we do that, then we will help that enterprise.

The CHAIRMAN. Thank you. I guess I would also say that it is living proof that little kids really are Petri dishes, if they are. I have accused mine of being that on occasion. [Laughter.]

Gentlemen, thank you very much for your time with us today. We are going to continue to pursue this until we get it right.

Mr. PARADISO. Thank you very much.

Mr. SLOAN. Thank you very much.

The CHAIRMAN. The hearing is adjourned.

[Whereupon, at 4:08 p.m., the committee was adjourned.]

APPENDIX

PREPARED STATEMENT OF SENATOR SUSAN COLLINS

Mr. Chairman, I want to commend you for holding this hearing to examine the current flu vaccine shortage and to discuss ways to remedy our vaccine supply problems in both the short and the long-term.

Influenza results in approximately 36,000 American deaths and more than 200,000 hospitalizations each year. It is particularly appropriate that the Aging Committee is holding today's hearing since the elderly are disproportionately affected, and are at particularly high-risk of complications and even death from influenza. Seniors account for nine out to ten deaths and one out of two hospitalizations related to the flu.

This issue is not new to the Aging Committee. I recall that, on September 28, the Senator from Idaho chaired a hearing in conjunction with National Adult Immunization Week at which both federal health officials and the CEO of Chiron (pronounced "Kyron") testified that the U.S. should have plenty of vaccine available for the upcoming flu season. Ironically, this was one week to the day before the announcement that United Kingdom health officials had revoked the Chiron Corporation's license to manufacture the flu vaccine in its Liverpool facility, effectively cutting our supply of vaccine in half.

Clearly, Congress must take action to increase and strengthen the nation's supply of flu vaccine. While long-term measures are needed to increase our nation's capacity to manufacture vaccine, I believe that action must also be taken without delay to maximize the value of the existing vaccine supply. This is particularly true given the fact that even the most aggressive efforts to increase supplies of new vaccine will have little effect on the current shortage due to the long period of time necessary to produce more vaccine.

To that end, on October 26, I joined Senator Jack Reed in sending a letter to Secretary Tommy Thompson urging that he do all that he can administratively to optimize the utilization of the existing vaccine and to increase the available supply. We were particularly concerned that the Centers for Disease Control not adopt a "one size fits all policy" and urged that they consider each state's unique needs in allocating new shipments of vaccine. I was therefore pleased by the Department's announcement on November 9 that they would be working with state health departments to ensure that the remaining vaccine reaches those people at highest risk for complications from influenza.

In addition, I have also signed on as a cosponsor of the Emergency Flu Response Act, which gives our health agencies the tools they need to respond to the current flu vaccine shortage and to maximize the effectiveness of our reduced vaccine stocks. I understand that the Chairman has also introduced legislation to improve our nation's preparedness to combat influenza. I therefore look forward to working with him next year on a comprehensive plan that addresses not just the short-term problems with this year's flu vaccine supply, but that also revitalizes our efforts to ensure adequate supplies of all vaccines.

Again, I commend the Chairman and thank him for holding this important hearing.

CDC RESPONSES TO QUESTIONS FROM SENATOR WYDEN

Question. What justification does CDC have for not buying the many doses of vaccine available from wholesalers in Europe? That vaccine is available now unlike the vaccine from manufacturers which may not be available till January, which may be too late to protect some of the highest risk patients.

Answer. In the United States, it is illegal to use any drug that is not approved by the Food and Drug Administration (FDA). Therefore, to allow treatment of pa-

tients with an unapproved drug, FDA may permit its use under an Investigational New Drug application (IND), which must be approved by FDA before an unapproved drug is released for use in the United States. These FDA requirements are designed to ensure the protection of human subjects and require that certain safety, efficacy, manufacturing, shipping, and storage process date be available.

The influenza vaccine available from Europe is not licensed for use in the United States. In order for it to be given to individuals in the United States, the manufacturer or some other sponsor must submit product information and an Investigational New Drug Application (IND) to FDA. FDA reviews the data and determines whether the product is safe for use in people. For more information about INDs, see http://www.fda.gov/cber/ind/ind.htm.

On December 7, 2004, the Health and Human Services (HHS) Secretary Tommy Thompson announced that the influenza vaccine manufactured in Germany was safe enough to be used in the United States and that as many as four million doses would be available to alleviate the U.S. shortage. Secretary Thompson announced that the government was immediately buying 1.2 million doses of the vaccine, called Fluarix, which will be available in January.

Question. Has CDC provided states or other entities assistance in locating doses available in the world market and what is CDC's role in helping these entities in making doses available in the U.S.?

Answer. Two manufacturers of influenza vaccines licensed for use in Europe have vaccine which is under review for use in the United States as Investigational New Drugs (IND). Because these vaccines are not licensed in this country, they will have to be administered under special protocols with written consent that must be approved by an Institutional Review Board (IRB) and the FDA. CDC is working with these companies to develop protocols for the use of these vaccines so they can be made available to states that choose to offer them under the CDC- and manufacturer-sponsored INDs. In addition, states that have identified and/or purchased vaccine from foreign distributors can choose to submit their own IND protocol to FDA for review and approval to allow them to import and administer these vaccines.

STATEMENT OF THE
AMERICAN COLLEGE OF PHYSICIANS
TO THE
SENATE SPECIAL COMMITTEE ON AGING
For the Record of the Hearing
"Liability, Licensing and the Flu Vaccine Market: Making Decisions Today to Prevent a Crisis Tomorrow"
November 16, 2004

The American College of Physicians (ACP) -- representing 116,000 physicians and medical students -- is the largest medical specialty society and the second largest medical organization in the United States. Internists provide care for more elderly and patients with chronic health conditions than any other medical specialty. As such, the College urges Congress and the Executive Branch to work together in a bipartisan fashion to address misdistribution and shortages of influenza vaccines. The current influenza vaccine shortage highlights many of the shortcomings of our existing system.

The development and use of vaccinations is one of the most successful and cost-effective public health initiatives in history. Vaccines reduce future medical costs and prevent the need for more expensive drugs. While high levels of immunization have been achieved in the U.S., especially among children, our current system of production and distribution cannot guarantee a stable supply of vaccines. This recurring problem brings into question whether the U.S. is prepared to manufacture and distribute vaccines in the case of an unexpected bioterrorist attack, let alone a potential outbreak of a number of routine diseases.

Going into this flu season, the public was assured that plenty of vaccine would be available to meet the nation's needs. The U.S. was expected to have 100 million doses of flu vaccine this year, up from 87 million last winter. Now, federal health officials expect to have only about 56 million doses of injectible vaccine and another one to two million doses of nasal flu vaccine spray.

ACP is gravely concerned about the impact these recurring shortages will have on the nation's health. Influenza, on average, results in 36,000 deaths and more than 200,000 hospitalizations each year in the U.S. While rates of infection are highest among children, rates of serious illness and death are highest among people over age 65 and people who have medical conditions, such as chronic diseases, that place them at increased risk for complications from influenza. Persons aged 65 or older account for more than 9 of 10 deaths and 1 of 2 hospitalizations related to influenza. According to the Department of Veterans Affairs, the nation loses $1.3 billion each year due to causes related to the flu, including extended hospital stays and a lack of productivity from missed work and school days.

The current flu vaccine shortage points to several inadequacies in the U.S. vaccine production and distribution system. For one, the U.S. production system relies on too few providers. In 2002, children were endangered and the risk of a serious outbreak increased when five vaccines that prevent eight childhood diseases were in short supply, forcing more than 40 states to ration these vaccines to children entering school. At the time, only four manufacturers produced vaccines for American children, just two of which were American companies. This year, the unexpected suspension of Chiron Corporation's license to manufacture flu vaccine left the U.S. with a single supplier of injectible vaccine.

The unwillingness of manufacturers to enter or remain in the vaccine market has much to do with uncertain returns on investment and the lack of government interventions to avert such problems. There is little economic incentive to manufacture flu vaccines since flu strains are constantly changing, doses cannot be used from year-to year, and manufacturers must bear all of the cost of surplus vaccines. As a result, manufacturers tend to produce fewer doses so as not to risk creating a costly surplus. In 2002, manufacturers lost approximately $120 million through unused vaccines. As a result, 12 million fewer vaccines were produced in 2003 to avoid repeating such a loss.

Because manufacturing cannot begin until new virus strains are identified and grown, it is difficult to stockpile flu vaccine or plan ahead for future flu seasons. ACP appreciates that the Department of Health and Human Services (DHHS) has taken steps to ensure that once the virus is identified, resources are in place to ramp up production and produce enough vaccine to protect U.S. residents as quickly as possible. However, the vaccine industry still relies on outdated technology. In a report released in September 2004, the Government Accountability Office (GAO) noted that the current U.S. system relies on a 50-year old method that uses specially harvested chicken eggs to produce licensed influenza vaccines. Food and Drug Administration (FDA) officials and vaccine manufacturers have stated that this production process cannot be shortened to less than the current 6 to 8 months given the existing technology and safety standards.

Manufacturers are also reluctant to produce vaccine because of the threat of lawsuits over vaccine safety. In 1986, a no-fault compensation system called the Vaccine Injury Compensation Program (VICP) was created to lower the legal risk to vaccine manufacturers and providers who administer vaccines, and to ensure that injured patients are rapidly and appropriately compensated. Recently, the VICP has become overwhelmed with new claims -- many of which have been found to lack merit. This has not only delayed consideration of legitimate claims, but caused the spill-over of costly lawsuits into our court system.

Despite the demonstrated effectiveness of vaccination in particular risk groups, our national distribution system also fails to ensure that high-risk patients will have access to vaccines first. Current distribution is based on the date the vaccine was ordered rather than who needs it most. If a manufacturer's production is disrupted, those providers who ordered vaccine from that manufacturer could experience shortages, while those who ordered vaccines from another manufacturer might not be affected at all. ACP is pleased

that in response to the current shortage, the CDC is recommending prioritization of vaccine for those at higher risk. However, the agency currently has no authority to mandate that the vaccine go to priority patients or to track where it ends up.

ACP Recommendations

Access to an adequate supply of flu vaccine is especially critical for physicians of internal medicine, since many of our patients qualify as high-risk for complications from influenza, due to either chronic health conditions or age. During previous flu seasons, much of the limited flu vaccine supply went to non-professional distributors, such as drugstores and grocery stores, who distributed the vaccine on a first-come first-serve basis, regardless of risk.

ACP appreciates that the DHHS is taking positive steps to address the current problem and keep the public informed of measures to prevent and treat the flu. We are pleased that a task force has been created to ensure that the flu vaccine and treatment medication goes to those who need it most and without any price gouging. We are also pleased that it includes members of the public health community, physicians, law enforcement and prosecutors, trade associations and advocacy groups. ACP thanks the CDC and Aventis Pasteur for working to identify providers of high-priority populations, including primary care and specialty physicians. Finally, ACP appreciates that the American Jobs Creation Act of 2004 (P.L. 108-357), recently signed into law, takes a first step in the direction of adding the flu vaccine to the VICP. Adding the flu vaccine to the VICP would provide limited liability protections for flu manufacturers, while assuring victims compensation for injuries.

Despite these positive efforts, ACP is concerned that our nation lacks a permanent mechanism to ensure that vaccines reach internists and other primary care physicians who have been clearly identified as providers who care for high-risk patients. To improve our nation's vaccination efforts and ensure that patients most in need can continue to access vaccines, ACP makes the following recommendations for immediate action and offers additional steps for the future:

Recommendations for Immediate Action

- To ensure that patients most in need receive the vaccine, manufacturers of the influenza vaccine, non-professional distributors of the vaccine, and appropriate government agencies should ensure that limited supplies of the vaccine are made available to clinicians and other licensed health care providers who provide regular patient care to high-risk individuals.
    - -In taking steps to ensure that limited vaccine supplies reach providers who serve high-priority populations, the CDC should continue to recognize the role of physicians of internal medicine in treating a disproportionately large number of seniors and patients with multiple, chronic conditions-- two patient categories that have historically been labeled by the CDC as high-risk. For many vulnerable patients, the physician's office is the best location to be

immunized, especially for patients who are unable to stand in line at grocery and drugstores, and who require careful monitoring.

- Local public health departments should have an aggressive plan in place to distribute vaccine to local providers with the greatest need.

- States should thoroughly investigate reports of price gouging involving the flu vaccine and prosecute those found to be taking advantage of the vaccine shortage.

- To comply with emergency orders issued by state or local governments mandating vaccine be administered only to persons of high risk, physicians should have access to clearly communicated prioritization requirements, distribution plans, and other instructions. Physicians should not be penalized for failure to follow emergency orders that are not clear and timely and do not provide for due process to resolve situations outside the physician's control.

Additional Recommendations

- The CDC should be given the authority to organize the distribution of vaccines and implement a concentrated response system, particularly in emergency situations.
  -Appropriate and adequate distribution plans should be formulated by the CDC prior to the start of a flu season. U.S. officials should not be scrambling for ways to modify the distribution system to make up for shortages as the flu season begins, as is the case this year.
  - A vaccine clearinghouse should be established to facilitate donation of vaccine to individuals at high risk of infection.
  -DHHS should be permitted to purchase vaccine from employers or wholesalers who are willing to sell it.

- Additional research and development to improve surveillance of strains and outbreaks and to improve current vaccine production methods should be encouraged.
  - Research funding should be increased to help develop alternatives to egg-grown influenza vaccines.

- The federal government should be required to build and maintain a six-month stockpile of prioritized vaccines to prepare our nation for vaccine shortages.

- The federal government should offer incentives to encourage more manufacturers to research and produce vaccines, such as tax incentives for vaccine manufacturers to expand production capabilities and guarantees that the government would purchase unused supply.

- Funding available for state and local efforts should be expanded to boost immunization rates among adults and adolescents who are underserved or at high risk for vaccine-preventable diseases.

-Funding should be authorized under the Public Health Service immunization program for the distribution of influenza vaccine to qualifying health care providers, including internists.

- Increase education and outreach efforts for upcoming flu seasons.

- Revise provisions governing the Vaccine Injury Compensation Program (VICP) to ensure that unwarranted litigation does not further destabilize our vaccine supply.

- Vaccines manufactured abroad should only be used in the U.S. if the FDA has certified their safety.

For many years, unavailability of vaccine products has presented a challenge to physicians and patients. The federal government must have a system in place to assure an adequate and safe supply of lifesaving vaccines in the event of a disruption in the expected supply. It is also critical that an adequate and appropriate distribution system be in place to ensure that the most vulnerable patients have access to vaccines before all others.

WHO OMS

Statement by the World Health Organization for the Senate Special Committee on Aging

16 November 2004

The WHO Role in Preparedness for Seasonal and Pandemic Influenza

Introduction

The draft HHS Pandemic Influenza Preparedness and Response Plan for the United States, issued in August 2004, underscores the importance of WHO' s global monitoring of influenza viruses and disease activity, and explains how this function is performed by WHO through an extensive network of laboratories worldwide. Information about circulating influenza viruses gleaned from this WHO global network allows the Centers for Disease Control and Prevention (CDC) to predict the potential impact of influenza on the United States population in any given year. The network gives vaccine manufacturers the information and "seed" viruses they need to produce the recommended new vaccine for each year's influenza season. It also functions as a sensitive early-warning system for detecting the emergence of new influenza viruses with pandemic potential.

As explained below, the public health need to keep a constant and close watch over the influenza situation arises from the highly unstable nature of influenza viruses. These genetically labile viruses constantly change in small ways, necessitating a new vaccine for each year's influenza season. In rare but recurring events, the influenza virus changes so dramatically that it ignites a pandemic, in which unusually severe influenza rapidly spreads to every continent. Influenza pandemics are invariably associated with great illness and absenteeism, increased numbers of deaths, and considerable social and economic disruption.

The WHO surveillance network has closely monitored the outbreaks of highly pathogenic avian influenza that have been reported since the start of 2004 in large parts of Asia. These outbreaks, caused by the influenza A(H5N1) virus, have brought the world closer to a pandemic than at any time since 1968, when the last of three pandemics during the 20th century occurred. Network laboratories, including CDC, have investigated the H5N1 influenza viruses from human cases, compared them with historical samples, and directly assisted affected countries with diagnostic support. CDC also investigated viruses from the first probable case of human-to-human H5N1 transmission. Altogether, eight network laboratories offer specialized diagnostic support for H5N1. The high quality of surveillance – of both viruses and human and animal cases – has given the world its first opportunity to undertake intensified preparedness measures on the brink of a pandemic.

The medical intervention of first-choice for reducing illness and deaths is the same for both seasonal and pandemic influenza: a vaccine. Global manufacturing capacity for all influenza vaccines is currently limited. Plant capacity is largely determined by the average annual use of vaccine for seasonal influenza, and this has traditionally been administered to groups at high risk of severe illness and life-threatening complications: the elderly, the immunocompromised, and persons with heart or lung disease. In contrast, a pandemic is characterized by almost universal susceptibility to severe disease caused by a completely new virus, requiring much broader vaccination strategies. Present global plant capacity is considered largely inadequate for meeting the huge surge in demand that will follow the onset of a pandemic. While the annual production of seasonal vaccines is a familiar and well-rehearsed procedure, the development and commercial production of a pandemic vaccine encounters several unique technical and regulatory problems. These problems are especially acute for the H5N1 virus, but all can be resolved. Industry innovations now under way as part of intensified pandemic preparedness, and supported by US government funding, hold promise to make the supply of seasonal vaccines more secure as well as improving pandemic preparedness.

The WHO network for global surveillance of influenza viruses

Of all the well-established infectious diseases, influenza – the invariable disease caused by a variable virus – numbers among the most worrisome. Scientists describe influenza viruses as sloppy, capricious, and promiscuous. Their labile and unpredictable nature is notorious. They are flexible and can mutate rapidly. As influenza viruses lack a proof-reading mechanism, the small errors that occur when the virus copies itself are left undetected and uncorrected. As a result, influenza viruses undergo constant stepwise changes in their genetic make-up. This strategy works well as a survival tactic for the virus: the speed with which new strains develop keeps populations susceptible to infection. Though small, the changes are sufficient to evade the defenses of the immune system. Populations protected, whether because of infection or vaccination, against one virus strain will not be protected when the next slightly different virus arrives. A new vaccine must therefore be produced for each winter season, when epidemics of influenza almost always occur.

As yet another feature, the genetic content of influenza viruses is neatly segmented into eight genes. This facilitates the most greatly feared event: the swapping of gene segments during co-infection with human and avian influenza viruses, creating a new virus subtype that will be entirely or largely unfamiliar to the human immune system. If this new "hybrid" virus were to contain the most feared mix of genes, namely those causing severe disease and those allowing easy human-to-human transmission, it will ignite a global pandemic. Pandemics are invariably associated with great morbidity, significant mortality, and considerable social and economic disruption. Of the three pandemics of the 20th century, the "Spanish flu" of 1918 is considered the most deadly disease event in the history of humanity, responsible for at least 40 million deaths globally. The pandemics of 1957 and 1968 were much milder. The 1957 pandemic travelled along sea lanes and spanned the globe within six months, causing at least 1 million deaths, while the 1968 pandemic was even milder.

Influenza surveillance is the oldest disease program at WHO. It was established in 1947 because of two concerns: the inevitable recurrence, at unpredictable intervals, of highly disruptive pandemics, and the significant health and economic impact of seasonal epidemics, which occur nearly every year. The objective at the outset was to obtain an ongoing representative picture, at the global level, of how the virus is changing and what these changes mean for human health. The program was set up as a network of laboratories commissioned to study circulating influenza viruses, collected from around the world, and to document changes in the viruses' genetic make-up. Within four years, the network included 60 laboratories in 40 countries. At that time, when the world was far less mobile and interdependent than now, public health authorities recognized influenza as a disease that cannot be mitigated without an international collaborative effort having a broad geographical scope. From its earliest years on, the network has operated as a model of international scientific collaboration to safeguard public health: virus strains are made freely available to other laboratories and to manufacturers the moment any unusual characteristics are detected.

Today, the WHO Global Influenza Surveillance Network consists of 111 national influenza centers located in 83 countries, and four WHO collaborating laboratories for influenza reference and research, located in London, Atlanta (CDC), Melbourne, and Tokyo. The national centers collect influenza viruses circulating in different parts of the world. These are then sent to the four collaborating laboratories for in-depth investigations. Apart from providing a composite global picture of changing influenza activity, this work allows WHO to issue advice, twice each year, on the composition of influenza vaccines considered most likely to confer protection against seasonal epidemics in both the northern and southern hemisphere. The WHO network has thus contributed greatly to the understanding of influenza epidemiology and assists manufacturers both by ensuring that influenza vaccines contain the most appropriate viruses and by providing them with high-yielding "seed" virus for vaccine production.

In a given year, around 200,000 samples are collected by the national centers, of which 6,500 are sent to the four laboratories for further in-depth investigation. Each year the CDC prepares a kit of reagents to assist the global network in determining the types of viruses in circulation. The results are reported directly to WHO. The four collaborating laboratories also store virus samples for historical comparisons and provide diagnostic support for countries experiencing unusual influenza cases, such as those caused by H5N1. At present, eight network laboratories, including the CDC, perform specialized diagnostic work on H5N1 viruses. Although all this work takes place quietly behind the scenes and receives little attention, it is universally regarded as a model of efficient surveillance and effective international collaboration.

The H5N1 situation in Asia: a pandemic in waiting?

Several events in recent months indicate that the complex ecology of influenza viruses may be changing in ways that favor the start of another influenza pandemic. The events have occurred in two waves. The first and most dramatic involved the largest outbreak of highly pathogenic avian influenza in poultry ever experienced anywhere in the world, resulting in the death or destruction of more than 120 million poultry. Prerequisites for the start of a pandemic were met when the causative agent, the H5N1 avian influenza strain, crossed the species barrier to infect humans, causing severe disease with high mortality. Fortunately, the virus has not yet adapted to allow efficient human-to-human transmission. In a second wave of events, fresh outbreaks, more human

cases, and new research have revealed that opportunities for such an adaptation to occur have become both broader and more permanent in nature.

Viewed together, these events call for a high level of alert and preparedness supported by specific actions on the part of individual countries, the international community, and WHO. Influenza pandemics are rare but recurring events. Unlike the case with SARS, which was stopped less than four months after the start of international spread, the rapid spread of influenza throughout the world cannot be stopped. Good health systems, good standards of living, and good levels of hygiene are no protection against a highly contagious airborne disease. Historically, global spread of influenza pandemics has been completed in around 6 to 8 months. Few other infectious disease threats demonstrate so vividly the need for international solidarity in the face of a shared threat.

Evolution of the present situation. Beginning in December 2003, outbreaks of highly pathogenic H5N1 avian influenza swept through eastern Asia, affecting eight nations and resulting in the death or destruction of more than 120 million domestic birds. The outbreaks were historically unprecedented in the size of the geographical area affected, the rapid spread within and between countries, and the devastating consequences for agriculture. Most of the eight affected countries had never before experienced an outbreak of highly pathogenic avian influenza in their histories.

In January 2004, human cases of H5N1 infection, characterized by severe illness with a high fatality, were reported in Viet Nam and Thailand – two countries with especially widespread outbreaks in poultry. This event greatly raised the level of public health concern and stimulated intense research efforts, fully supported by laboratories in the WHO influenza network. From January through March of this year, 35 human cases were reported, of which 24 were fatal. Epidemiological investigations linked most of these cases to direct contact with infected poultry. Studies found no evidence of efficient human-to-human transmission. The fact that so few human cases occurred in the midst of such widespread outbreaks in poultry indicates that the virus does not, at present, cross easily from poultry to humans.

Great efforts were made to end the outbreaks. Control measures were carried out with the objective of eliminating the virus from its poultry host. However, control – always difficult – was complicated by the large number of free-ranging poultry raised on small rural farms. In Viet Nam, for example, 80% of the population lives in rural areas where nearly every household maintains a free-ranging backyard flock of chickens or ducks. After a sharp decline in the number of reported outbreaks, disease activity began to increase in July, with China, Thailand, and Viet Nam reporting fresh outbreaks. Indonesia has also detected new outbreaks. In August, Malaysia reported its first-ever outbreak of the disease, becoming the 9th Asian country affected by highly pathogenic H5N1 this year. Though small, the outbreaks in Malaysia have continued through November, indicating the great difficult of ridding poultry of this disease.

New evidence increases concern. Although this recurrence of outbreaks has affected far fewer birds (325,000 in Thailand, 63,000 in Viet Nam), nine additional human cases, of which eight were fatal, were reported from August through October in Viet Nam (4) and Thailand (5), indicating a continuing threat to humans as well as to poultry. This second series of human cases also saw the first probable instance of human-to-human transmission within a family, which has fortunately not been repeated. To date, H5N1 has caused 44 cases, of which 32 were fatal. When all cases are viewed together, two features are striking: the very high number of deaths and the

overwhelming concentration of cases in previously healthy young adults and children over the age of 5. The average age of cases in Viet Nam is 14 years and, in Thailand, 20 years.

New evidence strongly suggests that the H5N1 virus is now endemic in the region, having established an entrenched ecological niche in poultry. It is also now known that infected domestic ducks can shed virus in its most deadly form, yet show no overt signs of illness, raising important questions about their role in the transmission cycle. As these ducks shed virus without giving the warning signal of visible illness, it has become difficult to give rural residents realistic advice on how to avoid infection. Several of the recent cases could not be traced to direct contact with dead or diseased poultry. With the virus is now permanently established in poultry in parts of Asia, the complete elimination of the virus in poultry will be extremely difficult if not impossible. The risk to humans will continue.

Other new studies show that the virus has increased its capacity to cause very severe disease in mammals and birds, and may be expanding its host range in mammals. In the most recent experimental work, domestic cats were infected with H5N1, developed severe disease, transmitted infection to other cats, and developed infection when fed infected chicken. In Thailand in October, H5N1 caused the death of more than 160 captive tigers – another species not previously considered susceptible to infection – fed on chicken carcasses.

The increasing detection of H5N1 in dead migratory birds adds weight to prior speculation about their role in spreading the disease, thus increasing the likelihood that the virus may be re-introduced to previously affected areas or spread to new ones. In 2003, H5N1 virus was isolated from diseased pigs on farms in southern China, marking the first time that natural infection of pigs with any virus in the H5 family has been documented. This is of particular concern. Pigs possess cells in their respiratory tract that allow them to be infected with both human and avian influenza viruses, making them the ideal "mixing vessel" for the swapping of genetic material between human and avian viruses. Previous studies have shown that H3N2, one of the two strains currently circulating in humans, is endemic in pigs in southern China. Conditions are therefore ripe for co-infection of pigs with human and avian viruses.

These findings strongly suggest that the H5N1 virus now has multiple opportunities to transmit to humans. They further suggest multiple opportunities for co-infection of humans or pigs with human and avian viruses, allowing an exchange of genetic material that could result in a new virus with pandemic potential. With the virus now entrenched in an ecological niche, and with humans, pigs, domestic cats, great cats, and possibly other mammalian species susceptible to infection, conditions are particularly favorable for the start of a pandemic. The timing of pandemics defies prediction, but the present situation is certainly the closest the world has come to an influenza pandemic threat since 1968. Unlike the situation in previous centuries when influenza pandemics caught the world by surprise, monitoring of the outbreaks in Asia has provided clear warning signals that a pandemic may be imminent.

As a result, the world now has an unprecedented opportunity to defend itself against a virus, with proven pandemic potential, before the chaos of a pandemic begins. The unpredictable nature of influenza viruses makes it impossible to know when the next pandemic will occur and which strain will cause it. It is nonetheless prudent for governments to actively engage now in pandemic preparedness.

Recommended actions for risk assessment and pandemic preparedness

Reducing risks. Reducing conditions that favor emergence of a new virus must remain the first priority. WHO is therefore urging ministries of health in affected and at-risk countries to:

- Heighten surveillance for unusual clusters of severe respiratory disease in humans and report all H5 infections to WHO. Recommended laboratory tests to identify influenza A/H5 virus are described in a WHO document available at: http://www.who.int/csr/disease/avian_influenza/guidelines/labtests/en/ When requested, WHO can support further laboratory investigations needed to identify the strain.

- Collaborate closely with veterinary and agricultural officials to ensure that outbreaks in poultry are promptly detected, reported, and contained, as such outbreaks also constitute a risk to national and international public health. WHO guidelines for influenza diagnosis and surveillance in animals are available at: http://www.who.int/csr/resources/publications/influenza/en/whocdscsrncs20025rev.pdf

- Routinely share H5N1 viruses isolated from animals and humans with laboratories in the WHO influenza network. Comparison of these viruses with historical specimens yields clues about the evolution of the virus. Analysis of currently circulating viruses also yields information needed for diagnostic reagents, made available by WHO to all countries, and for the preparation of a pandemic vaccine. When requested, WHO can arrange for the shipment of such viruses to network laboratories: http://www.who.int/csr/disease/avian_influenza/guidelines/referencelabs/en/

- Support WHO-coordinated studies on the natural history of H5N1 infection to improve the diagnosis and management of human cases.

Ministries of Health are urged to collaborate closely with officials in other sectors and to take a leading role when developments in these sectors pose a risk to human health. Recent findings call for research in affected countries to determine whether H5 viruses are present in pigs and other mammalian species and to define the epidemiological significance when this occurs.

Preparedness. Vaccines, the first line of defense for reducing morbidity and mortality, may not be available at the start of a pandemic and will remain in short supply throughout the first wave of international spread. To gain as much time as possible, WHO asks that ministries of health in countries with manufacturing capacity for influenza vaccines urgently seek ways to support clinical trials of pandemic vaccines. This has begun to happen in the US and in some other countries. In the absence of vaccines, antivirals could assume greater importance as a prophylactic and treatment tool, and countries should begin now to explore this option. At present, however, extremely limited supplies are further constrained by the absence of surge capacity for production, high price, and logistic difficulties.

Preparedness: Pandemic vaccines. Vaccines are considered the first line of defense for reducing the high morbidity and mortality invariably associated with influenza pandemics. While vaccines have never been available in past pandemics, the world now faces a much more favorable situation. Warned in advance, industry, regulatory authorities, and some governments are already preparing the groundwork to make pandemic vaccines available as an urgent preparedness measure.

The most important immediate steps are the establishment of optimal vaccine formulation based on clinical trials, and registration of pandemic vaccines with licensing agencies. Such registration, done with a "template" influenza subtype (eventually replaced by the actual pandemic strain), is a condition which every manufacturer must fulfil to produce pandemic vaccines as rapidly as possible, regardless of when the next pandemic occurs and which strain causes it.

If this work moves forward with appropriate speed, and if the present window of opportunity remains open sufficiently long, advance stockpiles of pandemic vaccine could be available for the first time in history. H5N1 – the most likely pandemic strain – is well-characterized, and a prototype virus for production of seed vaccine has already been made available by WHO laboratories to interested manufacturers.

Recent advances have made it possible to produce raw materials, in the form of bulk antigen, in advance. This option would allow rapid formulation of vaccines conferring at least some protection against H5N1 for use in an emergency. However, a pandemic vaccine suitable for mass administration cannot be produced prior to the onset of a pandemic, as vaccine content needs to match the actual pandemic strain. Advance supplies of at least some vaccine, conferring some degree of protection, would allow early intervention at the first signs that H5N1 is improving its transmissibility in humans. Orders for advance supplies are important, as they require manufacturing at commercial scale and thus allow a "dry run" of production technology; early identification of potential technical problems and other lessons learned can benefit all manufacturers. A WHO proposal to move forward with creating stockpiles of vaccine, for highly targeted use to slow international spread and thus allow more time to increase vaccine supplies, can work as a short-term incentive for industry and increase global preparedness.

All of the major influenza vaccine manufacturers are engaged in some activities to move candidate pandemic vaccines forward to the commercial production stage. The prospect of having at least some supplies of a pandemic vaccine ready in advance depends on solutions to well-known technical, regulatory, scientific, and practical problems. These problems were addressed at a high-level meeting on pandemic vaccines, convened by WHO in late November 2004. Participants from industry, regulatory agencies, and health ministries agreed that all these problems can be solved, if the urgency to do so is appreciated.

Current industry initiatives, encouraged and coordinated by WHO, are expected to reduce the time between the start of a pandemic and the start of commercial production from the previous 7 to 8 months to as little as 2 months. Each day of manufacturing gained represents an additional 5 million doses.

Preparedness: Increased manufacturing capacity. WHO is further recommending increased use of vaccines for seasonal epidemics of influenza as the best long-term incentive is to increase manufacturing for all influenza vaccines. Capacity to manufacture a pandemic vaccine is driven by the demand for vaccines for seasonal influenza. Increased use of seasonal vaccines gives countries experience in the logistics of vaccine administration, while also helping to reduce the estimated 250,000 to 500,000 deaths caused globally by seasonal influenza each year. At the same time, investments now being made in improved pandemic vaccine capacity will bring a yearly return in the form of a more secure supply of seasonal vaccines.

Presparedness: Antivirals. As a third preparedness measure, WHO is encouraging countries with adequate resources to consider stockpiling antivirals. These drugs are effective for

prevention and, if administered within 48 hours following onset of illness, for early treatment of influenza. In the early stage of a pandemic, when vaccine supplies are inadequate, they can be used to reduce morbidity and mortality, particularly in priority groups, as defined by national health authorities.

The large-scale use of antivirals was contemplated during a WHO consultation in March 2004 as a potential strategy for forestalling international spread at the start of a pandemic. This strategy could be used if the virus shows early signs that it is improving its transmissibility in humans, and if this change is detected quickly by a strong surveillance system.

WHO continues to explore the feasibility of establishing an international stockpile of antivirals for this purpose. This option is made problematic by the high costs of the drugs, the small quantities currently available, the absence of surge capacity, and a lack of data confirming the effectiveness of antivirals during a pandemic.

Preparedness: National pandemic preparedness plans

WHO continues to stress the importance of national pandemic preparedness plans, including access to vaccines and antivirals, strengthened human and animal surveillance systems, and contingency planning for hospital and other essential health services.

U.S. SENATOR PAUL STRAUSS
DISTRICT OF COLUMBIA (SHADOW)

OFFICE OF THE
United States Senator
FOR THE DISTRICT OF COLUMBIA

1 JUDICIARY SQUARE
SUITE 1000-S
WASHINGTON, D.C. 20001
VOICE: (202) 727-7890
FAX: (202) 727-9672

Statement of

Paul Strauss

United States Senator

District of Columbia (Shadow)

Submitted for the Record of the

HEARING OF THE

U.S. SENATE SPECIAL COMMITTEE ON AGING

"Liability, Licensing and the Flu Vaccine Market:

Making Decisions Today to Prevent a Crisis Tomorrow"

Tuesday, November 16, 2004

2:30 pm

Room 628, Dirksen Senate Office Building

Chairman Craig and members of this committee, I am Paul Strauss, the United States Senator for the District of Columbia. I would like to thank the committee for holding this hearing on this very important issue and for allowing me to enter a statement into the record on behalf of my Constituents, the great citizens of the District of Columbia.

Let me begin with an expression of my deepest concern about the vaccine shortage encountered this year and my hopes that this committee will find a solution for the upcoming years, to protect the people throughout the country and specifically within the District of Columbia.

This situation is serious. Last year 36,000 people died because of the flu and we do not want this to happen this year or in the years to come. This Committee is right to question why the public health system in the United States is not taking care of something that is so predictable and preventable. The flu is not a disease we are dealing with for the first time. According to one of the District of Columbia's most respected physicians, Dr. Jean El-Bayumi, Associate Professor of Medicine at George Washington University, the shortage of flu vaccine is a problem that to some extent, physicians deal with every single year. This year however, she has expressed a new concern, that this administration is using people's health for politics. From my review of the record, her concern is justifiable. Every year there is a flu season, yet every year there is not enough flu vaccine. As a result, people who could be protected by a safe vaccine die of the flu.

Last year 36,000 thousand people died. How many of them could have been saved if there was enough vaccine? How many could be saved this year? The flu and the shortage of flu vaccine is an identified problem. Unlike in the past however, this administration spent millions of dollars for homeland security but fails to protect its people from a known and severe biological threat. If the administration used only a small portion of the money it spends allocated for our homeland security to ensure that there is enough flu vaccine for every American, many lives could be saved and a biological hazard would cease to be a potential weapon of mass destruction. At a minimum, the administration should investigate spending money to subsidize the manufacture of this needed flu vaccine so that we would not have a shortage every year. The public's life and safety should not be left to the market forces controlled by a handful of vaccine manufacturers but, rather, it is the duty of this government to intervene for the public health and safety of this country. This administration has to make

sure that flu vaccine is produced in a reliable and safe way to protect the people of this country from the flu. Saving 36,000 lives a year must be an aim of the administration as a part of the country's homeland security preparations as well as our traditional medical care obligations.

A clinician at Georgetown University told my office that he meets with almost one hundred patients each day of which 50 percent need a vaccine. However, he does not have any vaccine to offer them: children, seniors, people with cancer, people with heart disease, people who need such a vaccine because getting the flu could seriously endanger their life. Some hospitals do have a better supply, while others have no vaccine at all. Shouldn't there be enough for all the people that need a vaccine? On November 16, 2004, Peter R. Paradiso, Vice President for new Business and Scientific Affairs of Wyeth Pharmaceuticals, testified before this committee and identified lawsuits as a problem and a reason why vaccine producers from overseas chose to sell their products in Europe instead of selling it in the US. However, since 1988 the Vaccine Injury Compensation Program, as a no-fault alternative to the traditional tort system for resolving vaccine injury claims, protects vaccine producers from claims against their products. We cannot let the divisive and partisan issue of tort reform cloud the clear need for reform.

You cannot spend millions of dollars on homeland security on one side and let thousands of people die of a known threat on the other side. It is the duty of this government to prevent such a threat. I would like to thank the Committee Chairman, and Ranking Member for giving me the opportunity to present testimony for the record on the behalf of my constituents in the District of Columbia. The issue at hand is an important one to all Americans. Finally let me thank one of my Legislative Assistants, Monika Spring, for her assistance in researching this issue and preparing this statement.

○